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PANCREATIC LITHIASIS ASSOCIATED WITH PANCREATIC INSUFFICIENCY AND DIABETES MELLITUS

REPORT OF TWO CASES

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Pancreatic lithiasis is a relatively rare pathologic entity. A careful study of the literature published before 1939 reveals a total of approximately 125 reported cases of the disease. According to Witherspoon,[1] until 1935 operation had been performed in only 28 cases and in but 4 of these had a diagnosis been made prior to operation.

It was our privilege to observe 2 patients with this disease who were admitted to the medical service of the Cincinnati General Hospital within the period of one month. The condition of the first patient was diagnosed during life and that of the second at autopsy. In the first case we were able to confirm the diagnosis by demonstrating a definite lack of pancreatic enzymes both in the duodenal fluid and in the feces. In addition to the usual management of a diabetic patient, we administered rather large amounts of a potent preparation of pancreatic enzymes and observed the favorable effect.

REPORT OF CASES

CASE 1.—The diagnosis was made during the life of the patient by roentgen examination and by the typical signs and symptoms of pancreatic lithiasis. The patient, Mrs. L. F., a 50 year old white woman, had spent most of her life in Tennessee. She was in good health until four years prior to her admission to the hospital. At that time she began to have typical signs and symptoms of diabetes mellitus. A physician informed her that she had diabetes, placed her on a special

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1. Witherspoon, J.: Pancreatic Lithiasis, South. M. J. **11**:1064, 1937.

diet and instructed her to take insulin. She did not adhere to the diet, nor did she take insulin. Shortly after this time she had an attack of severe, knifelike pain in the right upper quadrant of the abdomen, which radiated to the epigastrium and posteriorly to the right scapular region. At the same time she became nauseated, and her abdomen became distended with gas. Diarrhea occurred, with the passage of six to eight light yellow, soft, fatty stools, which contained undigested particles of food. The attack then subsided spontaneously, and the patient had no repetition of the episode for about six months, when a similar attack occurred. The attacks then became more frequent and of greater severity and duration. During the year preceding admission to the hospital attacks occurred on an average of

Fig. 1.—Lateral roentgenographic view of the abdomen in case 1, illustrating infiltration of calculi into the head, body and tail of the pancreas.

every two or three months. In the two weeks before admission she had four rather severe attacks. The attacks characteristically occurred about two hours after eating, the pain lasting for about three hours. The pain was not relieved by ingestion of food. The signs and symptoms of diabetes had persisted from the time of onset until the date of admission to the hospital. At the age of 9 years the patient suffered from malaria. When she was 32 she was operated on for "female trouble." The past history was otherwise of no significance.

Physical examination revealed emaciation and evidence of wasting. The temperature was 98.6 F., the pulse rate 84, the respiratory rate 20 and the blood pressure 110 systolic and 60 diastolic. She weighed 90 pounds (40.8 Kg.). The skin was dry, loose, inelastic and wrinkled. It had a yellowish brown color similar to that often associated with malignancy. The right kidney was palpable;

there were tenderness and muscle spasm in the right upper quadrant of the abdomen, but no mass could be felt there or in the epigastrium. A ventral hernia was present below the umbilicus, in the region of the scar from a pelvic operation. Physical examination gave otherwise essentially negative results.

Laboratory examination revealed a negative Kahn reaction of the blood and a red cell count of 4,450,000, with a hemoglobin value of 13.4 Gm. The white cell count and the differential count were within normal limits. Examination of the urine revealed a trace of albumin, a 3 plus reaction for sugar and a 1 plus reaction for acetone. The stool was voluminous, light tan, soft and oily, with many particles of grossly undigested meat and vegetables. Microscopic examination revealed many striated muscle fibers, vegetable fibers and fat globules. The blood sugar during fasting was 344 mg. per hundred cubic centimeters. A dextrose

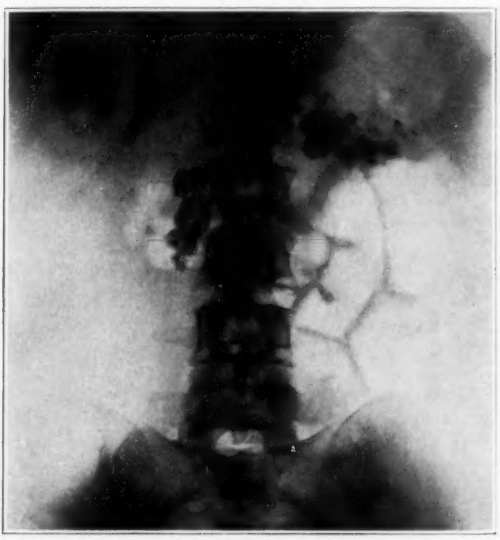

Fig. 2.—Anteroposterior roentgenographic view of the abdomen in case 1, showing calculi in the head, body and tail of the pancreas.

tolerance test was performed, 100 Gm. of dextrose being administered by mouth. One-half hour later the value for blood sugar was 400 mg. per hundred cubic centimeters; one hour later it was 488 mg.; two hours later, 500 mg., and three hours later, 513 mg. The cholesterol content of the blood was 125 mg.; the icteric index, 8; the value for blood phosphatase, 5.3 mg., and the blood phosphorus content, 2.8.

Analysis of the gastric contents revealed the presence of considerable mucus, a trace of bile and the absence of free acid in the fasting specimen, with the presence of 1.5 degrees of free acid, fifteen minutes after the intramuscular administration of histamine. The corresponding amounts of total acid were 3 degrees for the fasting specimen and 4 degrees for the fifteen minute specimen. Microscopic examination of the gastric contents revealed a few white and red cells and many particles of undigested food.

Repeated drainage of the gallbladder revealed A, B and C bile in normal quantities. No bile-stained cells were present, and cholesterol crystals were not detected. A large number of fat globules were present in all three types of bile.

Tests to detect quantitatively the deficiency of the pancreatic enzymes were performed on specimens of the duodenal juice, feces and urine. Tryptic activity of the duodenal juice as determined by the Gross method was under 1 unit, the average normal value being 2.5 units. The amylopsin content of the duodenal juice as determined by the Myers and Fine method was 2.5 units, the average normal amylolytic activity of duodenal juice being 40 units. Tryptic activity of a specimen of stool as determined by the Gross method was 8,000 units, as compared with an average normal value of 12,500 units. The amylase content of the stool as determined by the Myers and Fine method was 10,000 units, the normal value ranging from 30,000 to 60,000 units.[2] The amylase content of the urine was normal.

A series of roentgenograms of the gastrointestinal tract revealed diffuse areas of calcification in the region of the pancreas (figs. 1 and 2). No pancreatic calcifications could be demonstrated by fluoroscopic examination. Roentgenograms of the gallbladder did not give visualization of this organ.

The patient was placed on a diet for diabetic patients, high in carbohydrates and low in fats, and was given protamine zinc insulin in conjunction with a commercial preparation of pancreatic enzymes. The attacks of pain became much less frequent and relatively mild; the diarrhea disappeared, and the patient gained 10 pounds (4.5 Kg.). A short time after her discharge the blood sugar during fasting was 90 mg. per hundred cubic centimeters, and the urine was free of sugar and acetone.

Case 2.—Mrs. F. B., a 38 year old Negress, was admitted to the hospital in coma at 4:30 p. m. on March 13, 1938. The history, as obtained later from her husband, revealed that the patient had been receiving treatment for diabetes mellitus for several years at her home in Georgia. She had been taking insulin regularly. About three months before admission to this hospital she was in a hospital in Georgia for several weeks. At that time she was said to have been unconscious for five days. The patient came to Cincinnati ten days before being admitted to this hospital. She had made no provision for receiving insulin during her stay, and the day after her arrival she complained of sore throat and malaise. She went to bed and became delirious. Five days before she was brought to the hospital she lapsed into unconsciousness.

Physical examination on admission revealed emaciation. The eyeballs were soft and sunken. The heart rate was rapid, and the sounds were faint. Rales were heard at the bases of both lungs, but these were not marked. The abdomen was tense; no masses could be palpated. The patellar reflex was absent on both sides.

The red cell count and the value for hemoglobin were within normal limits. The white cell count was 12,800, with 94 per cent neutrophils, 5 per cent lymphocytes and 1 per cent monocytes. Urinalysis revealed albumin, 1 plus; acetone, 2 plus, and sugar, 4 plus, with a few white blood cells and occasional epithelial cells and hyaline and granular casts. The sedimentation rate was 24 mm. in one hour. The sugar content of the blood was 417 mg. per hundred cubic centimeters; the carbon dioxide-combining power was 17 volumes per cent, and the value for urea nitrogen was 55 mg. per hundred cubic centimeters.

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2. Levinson, S. A., and MacFate, R. P.: Clinical Laboratory Diagnosis, Philadelphia, Lea & Febiger, 1937.

On admission the patient received insulin, intravenous injections of fluids, lavage with a solution of sodium bicarbonate and application of heat to the body. However, she became progressively worse. The blood pressure fell from its highest reading of 72 systolic and 48 diastolic to a pressure which was too low to register. The blood sugar content shortly before death was 440 mg. per hundred cubic centimeters, with a carbon dioxide–combining power of 25 volumes per cent. The patient died five hours after admission.

The interesting postmortem observations as reported by Dr. R. Ritterhoff, of the department of pathology of this hospital, were in the pancreas. This organ was

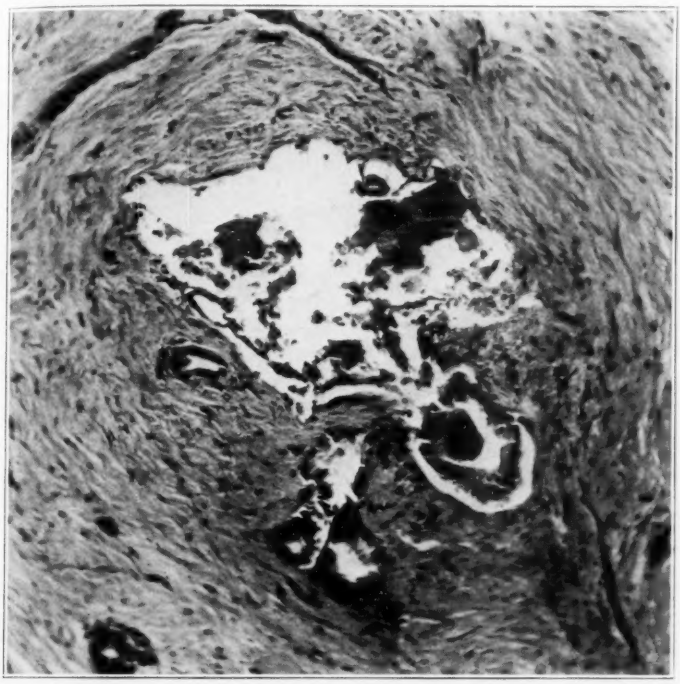

Fig. 3.—Microscopic section of the pancreas in case 2, illustrating extreme fibrosis with chronic interstitial inflammation, marked arteriosclerosis and arteriolosclerosis and dilated pancreatic ducts in which calcium is present. Note the pinching off of the acini and islets of Langerhans.

small and atrophic and was pink-white. It weighed 50 Gm. The tail and body appeared as a thin band, measuring 1.4 cm. in the greatest width. On palpation the pancreas was stony hard and very nodular. Cut sections of the nodular areas revealed a thin envelop of pancreatic tissue surrounding soft white calcaleous masses, which varied from 1 to 3 cm. in diameter. The pancreatic ducts were thickened, dilated and filled with the white calcareous masses. Microscopically, the pancreatic tissue showed considerable fibrosis, fatty degeneration and chronic

inflammation, with almost total lack of functioning pancreatic tissue (figs. 3 and 4). The kidneys revealed glycogenic degeneration.

COMMENT

The first case of pancreatic lithiasis in the literature was reported by de Graff in 1667 (cited by Seeger [2a]). He made no mention of associated glycosuria. In 1788 Cawley [3] reported a case of pancreatic lithiasis in which the patient had had diabetes mellitus during life. He

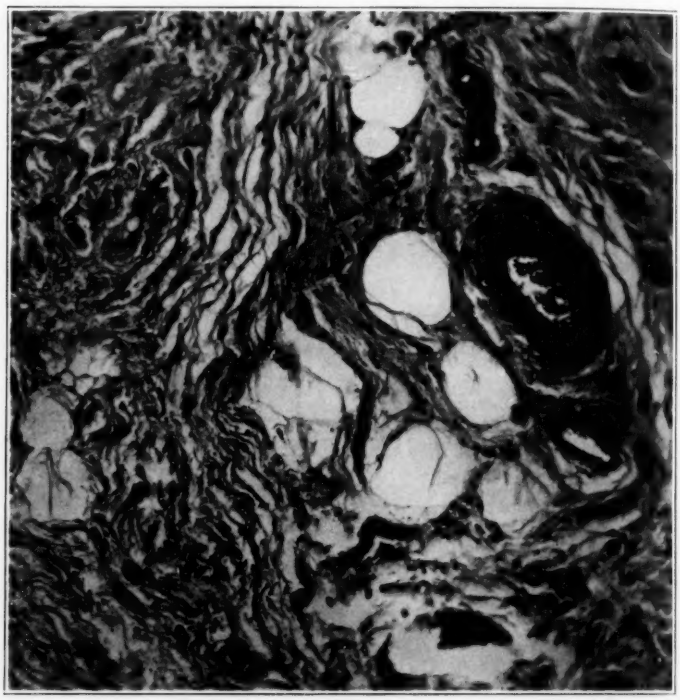

Fig. 4.—Microscopic section of the pancreas in case 2, illustrating extreme fibrosis with chronic interstitial inflammation and fatty invasion of the substance of the pancreas.

was the first to associate stones in the pancreas with diabetes. It remained for von Mering and Minkowski [4] in 1889 to demonstrate for

2a. Seeger, S. M.: Pancreatic Lithiasis, Radiology **10**:126, 1928.

3. Cawley, T.: A Singular Case of Diabetes, Consisting Entirely in the Quality of the Urine, with an Inquiry into the Different Theories of That Disease, London M. J. **4**:289, 1788.

4. von Mering, J., and Minkowski, O.: Diabetes mellitus nach Pankreasexstirpation, Arch. f. exper. Path. u. Pharmakol. **26**:371, 1889-1890.

the first time the true relationship between the pancreas and diabetes. It is interesting to note that Banting received the initial stimulation for his epoch-making discovery of insulin by reading the report of a case of pancreatic lithiasis made by Barron in 1920.[5] Barron reiterated what had previously been said by Opie,[6] that stones cause atrophy of the gland but that the islands of Langerhans remain intact, glycosuria being found only in the event that interstitial pancreatitis develops.

Among 7,402 necropsies performed at the Cincinnati General Hospital between Jan. 1, 1927 and Jan. 1, 1938, there were noted but 3 instances of pancreatic lithiasis. One of the patients had been admitted to the hospital in diabetic coma; the second had a fracture of the skull, and the third had lobar pneumonia. The last 2 patients had no history of previous glycosuria. In 1903 Oser [7] reported 70 cases of pancreatic lithiasis, in 24 of which glycosuria was demonstrated. Dillon [8] examined the autopsy records in 2,800 cases at the Philadelphia General Hospital and found only 2 cases of pancreatic lithiasis.

In 1936 Dr. J. G. Mayo [9] found a total of 25 proved cases of pancreatic lithiasis in the records of the Mayo Clinic. In 2 of these, the correct diagnosis was made during the life of the patient, and was confirmed at operation in the first case and at autopsy in the second. In 14 cases the lithiasis was discovered incidentally in the course of operations for other conditions. In 9 cases the diagnosis was made post mortem.

The cause of pancreatic lithiasis has not been determined with certainty. It has been stated that stasis plays an important role. Experiments on animals in which the main duct was tied did not result in the formation of stones. Nearly all of the stones that are found in the pancreas are composed of calcium carbonate. The secretion of the pancreas does not contain calcium carbonate, and for this reason it is thought that some factor, probably infection, alters the secretion, thus bringing about the formation of stones. The stones are usually found in the ducts and sometimes in cysts, in abscesses or scattered throughout the entire gland. Mayo [9] divided pancreatic stones into two types: first, true stones occurring in the ducts, and second, false stones repre-

5. Barron, M.: Relation of Islets of Langerhans to Diabetes, Surg., Gynec. & Obst. **31**:437, 1920.

6. Opie, E. L.: Diabetes Mellitus Associated with Hyaline Degeneration of the Islands of Langerhans of the Pancreas, Bull. Johns Hopkins Hosp. **12**:263, 1901.

7. Oser: Disease of the Pancreas, in Nothnagel, H.: Practical Diseases of the Liver, Philadelphia, W. B. Saunders Company, 1903, vol. 3, pp. 11-303.

8. Dillon, E. S.: Report of Two Cases Showing Glycosuria Following Obstruction of the Pancreatic Ducts, Bull. Ayer Clin. Lab. **8**:35, 1924.

9. Mayo, J. G.: Pancreatic Calculi, Proc. Staff Meet., Mayo Clin. **11**:456, 1936.

senting calcification of the parenchyma following pancreatitis. He stated the belief that disease of the biliary tract is the causative agent in most cases. About 75 per cent of the cases reported have occurred in men. The largest solitary stone found was 2.5 inches (6.4 cm.) in diameter.

Of the symptoms, the most important and most common is pain. The pain is present in the epigastrium, sometimes to the right and sometimes to the left of the midline and often radiates posteriorly. Many patients complain of pain apparently similar to that which occurs in biliary colic. Colicky epigastric pain was present in 19 of 29 cases collected by Ackman and Ross.[10] During the attacks of pain, the patients often have diarrhea; the stools are light tan, greasy and spongy, and contain much grossly undigested food. These attacks may be accompanied by nausea and vomiting. Nearly all the patients complain of loss of weight. In a few cases jaundice has been found. Studies of enzymes have revealed marked diminution in pancreatic ferments. Other observations reported include stones in the stool, cutaneous pigmentation, a palpable mass in the epigastrium and a history of duodenal ulcer. These conditions do not occur with sufficient frequency to be of much diagnostic significance.

Roentgen examination is the most important aid in making the diagnosis during the life of the patient. In some cases the stones cannot be visualized, thereby making diagnosis difficult. Careful roentgen examination of the abdomen during visualization studies of the gallbladder would aid in making the diagnosis more frequently. Since many of the patients complain of pain similar to that in disease of the gallbladder, the taking of roentgenograms is usually limited to the right upper quadrant of the abdomen. In such cases the diagnosis may be missed. On the other hand, a flat roentgenogram of the abdomen taken before the administration of barium sulfate will usually reveal any stones which may be present in the pancreas. As pointed out by Hoechstetter,[11] the presence of an opaque medium, such as barium, in the stomach and intestines almost entirely obscures the site of the pancreas; hence the importance of taking a roentgenogram before the administration of the opaque meal. Stones in the region of the pancreas must be differentiated from renal lithiasis, calcified lymph nodes and cholelithiasis. It is of interest that in spite of the clear demonstration of the stones by a roentgenogram, it may be impossible to visualize them with the fluoroscope, even after their exact location is known. We observed this to be true in our first case.

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10. Ackman, F. F., and Ross, A.: Pancreatic Lithiasis, Surg., Gynec. & Obst. **55**:90, 1932.

11. Hoechstetter, S.: Pancreatic Lithiasis, Am. J. Roentgenol. **37**:33, 1937.

Contrary to the common belief that surgical treatment of this condition is fraught with danger, only 2 of 26 patients operated on died. In neither of these cases was fat necrosis or peritonitis the cause of death.[2a]

SUMMARY

Approximately 125 cases of pancreatic lithiasis had been reported in the literature before 1939. Two cases are presented in this report. The signs and symptoms of pancreatic lithiasis may simulate closely those of disease of the gallbladder. The diagnosis was made during the life of the patient in 1 case and at autopsy in the other. Diagnosis may be made more frequently during life by careful roentgen examination of the abdomen before the administration of barium.

THE LEVEL OF IODINE IN THE BLOOD

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Roger's "Practica," written about 1170, prescribed ashes of sponge and seaweed for goiter;[1] yet knowledge of the therapeutic value of iodine products in treatment of this disease and of the metabolism of iodine within the body has been developed only within the present century. Clinical and experimental evidence points to the fact that one of the primary functions of the thyroid gland concerns the metabolism of iodine. It is essential, therefore, to acquire as great an insight as possible into the biochemistry of iodine in normal and in goitrous persons. Investigations of the level of iodine in the blood have yielded information of value. The present communication deals with the development of knowledge of the concentration of iodine in the blood together with an analysis of a series of values for blood iodine in 1,078 consecutive patients with clinical hyperthyroidism and in 745 persons without evidence of thyrotoxicosis.

The quantitative estimation of the iodine content of the blood is not an easy procedure. This fact is evident from the numerous methods of analysis in the literature.[2] Many investigators experience difficulty in applying the method outlined by another worker and accordingly

From the Research Foundation and the Department of Surgery, the Lahey Clinic.

1. Garrison, F. H.: An Introduction to the History of Medicine, ed. 3, Philadelphia, W. B. Saunders Company, 1922, pp. 141-142.

2. (*a*) Bourcet, P.: Recherche et dosage colorimétrique de petites quantités d'iode dans les matières organiques, Compt. rend. Acad. d. sc. **128**:1120-1122, 1899. (*b*) Hunter, A.: The Determination of Small Quantities of Iodine with Special Reference to the Iodine Content of the Thyroid Gland, J. Biol. Chem. **7**:321-349, 1909. (*c*) Blum, F., and Grützner, R.: Methoden der Jodbestimmungen in organischen Substanzen, Ztschr. f. physiol. Chem. **85**:429-470, 1913. (*d*) Kendall, E. C.: Determination of Iodine in Connection with Studies in Thyroid Activity, J. Biol. Chem. **43**:149-159, 1920. (*e*) McClendon, J. F.: The World's Supply of Iodine in Relation to the Prevention of Goitre, Science **56**:269-270, 1922. (*f*) von Fellenberg, T.: Das Vorkommen der Kreislauf und der Stoffwechsel des Jods, Ergebn. d. Physiol. **25**:176-363, 1926. (*g*) Leitch, I., and Henderson, J. M.: The Estimation of Iodine in Food Stuffs and Body Fluids, Biochem. J. **20**:1003-1007, 1926. (*h*) Pfeiffer, G.: Ueber ein neue Schnellbestimmung von organisch gebundenem Jod, Biochem. Ztschr. **195**:128-133, 1928. (*i*) Kuhn, P., and Loeser,

devise a modified or a new technic. In some instances simplicity and rapidity have been the reasons for developing another method. In estimating the iodine content of the blood, one of two principles is usually followed. The first is referred to as the open combustion method.

A.: Einfache Schnellmethode zum quantitativem Nachweis von organisch gebundenem Jod in Körperflüssigkeiten, Arch. f. exper. Path. u. Pharmakol. **131**:262-267, 1928. (*j*) Jochman, E.: Ein Beitrag zur von Fellenbergschen Jodbestimmungsmethode, Biochem. Ztschr. **194**:454-460, 1928. (*k*) McClendon, J. F.: The Determination of Traces of Iodine, J. Am. Chem. Soc. **50**:1093-1099, 1928. (*l*) Lunde, S., and Closs, K.: Determination of Iodine in Blood, Norsk mag. f. lægevidensk. **89**:500-506, 1928. (*m*) Pincussen, L., and Roman, W.: Gemeinsame Bestimmung der Halogene in organischen Substanzen, Biochem. Ztschr. **207**:416-429, 1929. (*n*) Reith, J. F.: Die Mikrobestimmung von Jodiden neben anderen Salzen, ibid. **216**:249-268, 1929. (*o*) Glimm, E., and Isenbruch, J.: Ueber die Bestimmung kleinster Jodmengen, ibid. **207**:368-376, 1929. (*p*) Turner, R. G.: A Micro Colorimetric Method for the Quantitative Estimation of Iodine in Blood, J. Biol. Chem. **88**:497-511, 1930. (*q*) Aitken, A. A.: Improved Method for the Determination of Iodine in Blood, Biochem. J. **24**:1456-1459, 1930. (*r*) Scheffer, L.: Mikro-jod-bestimmung in organischen Substanzen, Biochem. Ztschr. **228**:426-436, 1930. (*s*) Schwaibold, J., and Harder, B.: Die Bestimmung des Jods in biochemischen Materialien, ibid. **240**:441-453, 1931. (*t*) Remington, R. E.; McClendon, J. F., and von Kolnitz, H.: The Determination of Traces of Iodine: Further Refinements in Technic, J. Am. Chem. Soc. **53**:1245-1249, 1931. (*u*) Elmer, A. W.: Zur Vereinfachung der Mikrojodbestimmung, Biochem. Ztschr. **248**:163-167, 1932. (*v*) Davis, C. B., and Curtis, G. M.: The Quantitative Determination of the Iodine Content of Blood, J. Lab. & Clin. Med. **18**:24-29, 1932. (*w*) Baumann, E. J., and Metzger, N.: The Determination of Iodine in Blood, Foods and Urine, J. Biol. Chem. **98**:405-416, 1932. (*x*) Allot, E. N.; Dauphinee, J. A., and Hurtley, W. H.: The Determination of Small Quantities of Iodine in Blood, Biochem. J. **26**:1665-1671, 1932. (*y*) Widman, E.: Die Methodik der Blutjodbestimmung, Biochem. Ztschr. **254**:223-228, 1932. (*z*) Leipert, T.: Die Bestimmung kleinster Jodmengen inorganischen Material, ibid. **261**:436-443, 1933. (*a'*) Perkin, H. J.: Determination of Iodine in Blood, Biochem. J. **27**:1078-1081, 1933. (*b'*) Eyckerman, J.: Eine Mikrobestimmungsmethode des Jods im Blut und anderen flüssigen oder verflüssigten organischen Produkten, Ztschr. f. Kinderh. **54**:435-439, 1933. (*c'*) Phillips, F. J., and Curtis, G. M.: Blood Iodine Studies: IV. The Clinical Determination of Iodine in Blood, Urine and Feces, Am. J. Clin. Path. **4**:346-353, 1934. (*d'*) McCullagh, D. R.: A New Method for the Determination of Iodine, J. Biol. Chem. **107**:35-44, 1934. (*e'*) Harvey, C. O.: Determination of Iodine in Biological Substances, Medical Research Council, Special Report Series, no. 201, London, His Majesty's Stationery Office, 1935. (*f'*) Trevorrow, V., and Fashena, G. J.: The Determination of Iodine in Biological Material, J. Biol. Chem. **110**: 29-38, 1935. (*g'*) Wilmanns, H.: Zur Methodik der Mikrojodbestimmung in biologischen Material, Biochem. Ztschr. **289**:41-51, 1936. (*h'*) Hamilton, R. H.: Improvements in Technic for the Determination of Microgram Quantities of Iodine, J. Am. Chem. Soc. **58**:1592-1594, 1936. (*i'*) Fashena, G. J., and Trevorrow, V.: A Note in the Determination of Iodine in Biological Material, J. Biol. Chem. **114**:351-355, 1936. (*j'*) Stevens, C. D.: Determination of Iodine in Biological Material, J. Lab. & Clin. Med. **22**:1074-1079, 1937.

Procedures employing open combustion are held in disfavor by some workers because of the susceptibility to loss of iodine and to contamination from the environment.[3] The second principle is recognized as the closed system, the destruction of the organic material being done within a closed chamber. Methods involving the latter system have likewise been the subject of criticism.[4] It is not our purpose to detail the advantages or the shortcomings of either principle. In approximately 25,000 analyses of blood iodine we have used an open combustion method [2a'] and have found it to be satisfactory for our purposes. We believe that any investigator who will carefully adhere to the technic of any of the so-called standard procedures for determining the iodine content of the blood can obtain results which are relative one to another.

In 1900 Gley and Bourcet,[5] using Bourcet's method,[2a] demonstrated the presence of iodine in the blood of dogs. Using a liter of blood for analysis, they secured an average value of 5.5 micrograms per hundred cubic centimeters. The accuracy of this figure is recognized. Gallard,[6] using the same method, studied the level of iodine in the blood of rabbits after the application of iodine to the skin. In 1914 Blum and Grützner [7] expressed doubt of the existence of iodine as a normal constituent of the blood of human beings. Cameron [8] in 1914 and 1915, using the method of Hunter,[2b] was unable to detect iodine in the blood of dogs and of rabbits. These negative results can be attributed to the small amount of blood (0.5 Gm.) used for a single estimation. Twenty years after Gley and Bourcet's original discovery, Kendall and Richardson [9] confirmed the presence of iodine in blood. Using 100 Gm. of blood from dogs for analysis, they reported an average value of 13 micrograms per hundred grams.

From this work it was evident that iodine occurred naturally in normal blood. However, the large amount of blood required for one determination was a drawback in studying the level of blood iodine in human beings. This obstacle was overcome by von Fellenberg, who

3. Möbius, W.: Vergleichende Blutjoduntersuchungen bei trockener und fenchter Veraschung, Biochem. Ztschr. **253**:275-278, 1932.

4. Doering, H.: Die Blutjodwerte, Biochem. Ztschr. **280**:442-447, 1935.

5. Gley, E., and Bourcet, P.: Presence de l'iode dans le sang, Compt. rend. Acad. d. sc. **130**:1721-1724, 1900.

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7. Blum, F., and Grützner, R.: Kommt Jod im Blut vor? Ztschr. f. physiol. Chem. **91**:450-464, 1914.

8. Cameron, A. T.: Contributions to the Biochemistry of Iodine: The Distribution of Iodine in Plant and Animal Tissues, J. Biol. Chem. **18**:335-379, 1914; **23**:1-39, 1915.

9. Kendall, E. C., and Richardson, F. S.: Determination of Iodine in Blood and Tissues, J. Biol. Chem. **43**:161-170, 1920.

reported in 1926 [2f] the first micromethod by means of which the quantity of iodine in 10 cc. of blood could be estimated. The development of this technic was a stimulus to other investigators, and many studies on blood iodine appeared in the literature. Probably the most comprehensive of these was the work by Veil and Sturm,[10] which showed that the average level of blood iodine in normal human beings was 12.8 micrograms per hundred cubic centimeters in the summer and 8.3 micrograms per hundred cubic centimeters in the winter. This observation was confirmed by Maurer and Diez,[11] and further evidence of a seasonal variation in the level of iodine in the blood was reported by Nitzescu and Binder [12] and Davis, Curtis and Cole.[13] On the other hand, Scheringer [14] was unable to discern a seasonal variation in the iodine content of the blood, although he noted that a dietary deficiency of iodine resulted in a decrease in the iodine in the blood. These findings were in keeping with the work of Seidell and Fenger,[15] who had previously reported a seasonal variation in the iodine content of the thyroid gland of animals. Jansen and Robert [16] reported the normal range of values for blood iodine in human beings to be from 12 to 14 micrograms per hundred cubic centimeters; they noted that from 70 to 90 per cent of the total blood iodine was in the plasma. In a monograph on the biochemistry of iodine Orr and Leitch [17] reported normal values for blood iodine to be from 6 to 8.4 micrograms per hundred cubic centimeters. Certain of these studies were the subject of criticism by Blum.[18]

10. Veil, W. H., and Sturm, A.: Beiträge zur Kenntnis des Jodstoffwechsels, Deutsches Arch. f. klin. Med. **147**:166-223, 1925.

11. Maurer, E., and Diez, S.: Untersuchungen über das Vorkommen von Jod in menschlichen und tierschen Organismus, München. med. Wchnschr. **73**:17, 1926.

12. Nitzescu, I. I., and Binder, E.: Iodemie normale: Variations saisonniers; iodemie des goitreux, Compt. rend. Soc. de biol. **108**:279-280, 1931.

13. Davis, C. B.; Curtis, G. M., and Cole, V. V.: Blood Iodine Studies: II. The Normal Iodine Content of Human Blood, J. Lab. & Clin. Med. **19**:818-830, 1934.

14. Scheringer, W.: Beitrag zur Kenntnis des Blutjodspiegels beim Weibe unter physiologischen Bedingungen, Arch. f. Gynäk. **143**:319-337, 1930.

15. Seidell, A., and Fenger, F.: Seasonal Variations in the Iodine Content of the Thyroid Gland, J. Biol. Chem. **13**:517-526, 1912-1913.

16. Jansen, W. H., and Robert, F.: Die Jodfrage beim Kropfproblem, Deutsches Arch. f. klin. Med. **157**:224-246, 1927.

17. Orr, J. B., and Leitch, I.: Iodine in Nutrition, Medical Research Council, Special Report Series, no. 123, London, His Majesty's Stationery Office, 1929.

18. Blum, F.: Gebt es einen von der Schilddrüse abhängigen Jodspiegel des Blutes? Schweiz. med. Wchnschr. **8**:808-813, 1927.

Some interest has been taken in the physiologic variations of the level of iodine in the blood. Maurer and Diez,[19] Maurer [20] and Scheringer [14] reported that an increase in blood iodine occurred at the menstrual period in normal women. Maurer [20] noted an elevation in the blood iodine during the later stages of pregnancy. Bokelman and Scheringer [21] concurred with this observation. In addition, Scheringer [22] reported that an iodine-free ovarian extract was capable of increasing the iodine content of the blood. Hirsch [23] stated the belief that the periodic fluctuations in blood iodine in menstruating women were indicative of a thyroid-ovarian relation. Leipert [24] stated that the normal blood iodine level was 13 ± 4 micrograms per hundred cubic centimeters, irrespective of sex, age or season. He also stated that the blood iodine level in women was influenced by menstruation and pregnancy. A cyclic excretion of iodine in the urine of menstruating women has been reported by Cole and Curtis.[25] Presumably this reflects a fluctuating level of iodine in the blood. With the apparent existence of many minor fluctuations in the level of iodine in blood, the exactitude of such physiologic variations remains to be established. In our studies, although variations in the iodine content of the blood of individual persons have been observed and attributed to season, to the menses or to pregnancy, such observations are not consistent to the degree that they may be considered applicable in all instances.

With certain factors effecting minor changes in the level of iodine in the blood, the greatest deviation from normal was believed to occur in patients with clinical hyperthyroidism. Veil and Sturm [10] observed that the blood iodine in cases of exophthalmic goiter varied from 21 to 70 micrograms per hundred cubic centimeters. Biilmann,[26] reported a

19. Maurer, E., and Diez, S.: Zur Kenntnis des Jods als biogenes Element; Ueber Wachstums beschleunigung an jungen Ratten bei Verfütterung jodangereicherter Kost an das laktierende Muttertier, Biochem. Ztschr. **182**:291-300, 1927. Scheringer.[14]

20. Maurer, F. E.: Ueber den Jodgehalt des Blutes und seine Veränderungen in Menstruation und Gravidität, Arch. f. Gynäk. **130**:70-79, 1927.

21. Bokelman, O., and Scheringer, W.: Beitrag zur Kenntnis der Schilddrüsenfunktion und des Jodstoffwechselse in der Gestation, Arch. f. Gynäk. **143**:512-536, 1931.

22. Scheringer, W.: Experimentelle Beeinflussung des Jodstoffwechsels durch Corpus-luteum-Hormon, Arch. f. Gynäk. **146**:248-260, 1931.

23. Hirsch, O.: Ueber Beziehungen zwischen Eierstock und Schilddrüse bei der Basedowischen Krankheit, Deutsches Arch. f. klin. Med. **171**:44-51, 1931.

24. Leipert, T.: Zur Kenntnis des physiologischen Blutjodspiegels, Biochem. Ztschr. **270**:448-454, 1934.

25. Cole, V. V., and Curtis, G. M.: Cyclic Variations in Urinary Excretion of Iodine in Women, Proc. Soc. Exper. Biol. & Med. **31**:29-30, 1933.

26. Biilmann, G.: Iodine Contents of Blood Especially in Exophthalmic Goiter, Hospitalstid. **74**:395-404, 1931.

series of values for blood iodine in normal persons and in patients with nontoxic goiter and with hyperthyroidism. Although an overlapping in the range of the results for the different groups existed, Biilmann's observations indicated that the estimation of the iodine in the blood was of value in the diagnosis of thyrotoxicosis. Nuernbergk and Widmann [27] stated the belief that the blood iodine level was elevated in all patients with disturbances of the vegetative nervous system, including exophthalmic goiter. Schittenhelm and Eisler [28] reported a consistent elevation of the blood iodine level of from 15 to 90 micrograms per hundred cubic centimeters in patients with exophthalmic goiter. They also noted an elevation in the blood iodine of normal persons after the injection of epinephrine, whereas in patients with exophthalmic goiter the findings were reversed. Breitner [29] observed an increase in blood iodine in patients with hyperthyroidism, and in these patients the seasonal variation was the converse of that previously reported for normal persons.[10] Curtis, Davis and Phillips [30] concluded from their studies that a relation existed between the level of blood iodine and the degree of activity of the thyroid gland. Curtis, Cole and Phillips; [31] Elmer and Schepps; [32] Scheffer and von Megay; [33] Sturm, Plotner and Maas; [34] McCullagh,[35] and McCullagh and McCullagh [36] presented evidence favoring the diagnostic significance of estimating the blood iodine in diseases related to the thyroid gland. From the aforementioned work, the general impression prevailed that the blood iodine level was consistently elevated in patients with thyrotoxicosis despite the lack of correlation with the increment in the basal metabolic rate.

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27. Nuernbergk, H., and Widmann, E.: Blutjoduntersuchungen bei Vegetativ-Stigmatisierten, Klin. Wchnschr. **10**:1712-1713, 1931.

28. Schittenhelm, A., and Eisler, B.: Der Blutjodspiegel in seiner pathologisch-physiologischen und klinischen Bedeutung, Klin. Wchnschr. **11**:6-9, 1932.

29. Breitner, B.: Blutjodwerte und Jahreszeit, München. med. Wchnschr. **79**: 513-514, 1932.

30. Curtis, G. M.; Davis, C. B., and Phillips, F. J.: Significance of the Iodine Content of Human Blood, J. A. M. A. **101**:901-905 (Sept. 16) 1933.

31. Curtis, G. M.; Cole, V. V., and Phillips, F. J.: The Blood Iodine in Thyroid Disease, West. J. Surg. **42**:435-488, 1934.

32. Elmer, A. W., and Schepps, M.: The Iodine Content of Blood and of Urine and the Basal Metabolic Rate: Their Value in the Diagnosis of the Function of the Thyroid Gland, Acta med. Scandinav. **82**:126-136, 1934.

33. Scheffer, L., and von Megay, L.: Jodstoffwechsel bei Kropfträgern, Klin. Wchnschr. **14**:1360-1362, 1935.

34. Sturm, A.; Plotner, K., and Maas, K.: Zur Blutjodfrage, Biochem. Ztschr. **280**:396-412, 1935.

35. McCullagh, D. R.: Studies in Blood Iodine by the Use of a New Chemical Method, Cleveland Clin. Quart. **2**:15-37, 1935.

36. McCullagh, E. P., and McCullagh, D. R.: Clinical Experiences in the Use of Determinations of Blood Iodine, Arch. Int. Med. **57**:1061-1066 (June) 1936.

In contrast to the views previously stated, Turner [37] reported normal values for blood iodine in 5 (one third) of 15 cases of clinical hyperthyroidism. Veil and Sturm [10] had previously noted the presence of normal blood iodine in 3 patients with exophthalmic goiter; the results were attributed to treatment with digitalis and quinine. More recently Perkin, Brown and Lang [38] and Perkin, Lahey and Cattell [39] observed the regular occurrence of normal values for blood iodine in about 30 per cent of all cases of clinical hyperthyroidism. Perkin [40] presented additional evidence to indicate that patients with thyrotoxicosis whose blood iodine content was normal were usually more refractory to surgical treatment. Somewhat later Perkin and Hurxthal [41] and Perkin and Cattell [42] reported a greater tendency to recurrent hyperthyroidism after subtotal thyroidectomy in patients with exophthalmic goiter who had a normal blood iodine level prior to operation.

Since in clinical hyperthyroidism (exophthalmic goiter and adenomatous goiter with hyperthyroidism) an increase in the level of iodine in the blood is usual, a subnormal level might be anticipated in patients with myxedema. Although results on a large group of cases are lacking, Curtis, Cole and Phillips; [31] Elmer and Schepps,[32] and Sturm, Plotner and Maas [34] have reported low values for blood iodine in patients with this condition. It would seem that the determination of the level of iodine in the blood is of questionable significance for diagnostic purposes in cases of myxedema because normal persons without evidence of thyroid insufficiency but with a subnormal blood iodine level are often observed. The fact that the average value for blood iodine in patients with myxedema is appreciably less than the average in normal persons is evidence favoring a relative deficiency of iodine-containing products secreted by the thyroid gland in this condition.

As an increase in the urinary excretion of iodine usually reflects an increase in the level of iodine in the blood, certain results of

37. Turner, R. G.: Iodine Content of Certain Pathological Bloods in a Goitrous Region, Proc. Soc. Exper. Biol. & Med. **29**:1294-1296, 1932.

38. Perkin, H. J.; Brown, B. B., and Lang, J.: Blood Iodine Content of Normal and Thyrotoxic Individuals: Iodine Tolerance Test, Canad. M. A. J. **31**:365-368, 1934.

39. Perkin, H. J.; Lahey, F. H., and Cattell, R. B.: Blood Iodine Studies in Relation to Thyroid Disease: Basic Concept of the Relation of Iodine to the Thyroid Gland; Iodine Tolerance Test, New England J. Med. **214**:45-52, 1936.

40. Perkin, H. J.: The Value of Blood Iodine Estimations in the Treatment of Clinical Hyperthyroidism, S. Clin. North America **16**:1509-1511, 1936.

41. Perkin, H. J., and Hurxthal, L. M.: The Blood Iodine Level Before and After Subtotal Thyroidectomy for Hyperthyroidism, New England J. Med. **215**: 698-700, 1936.

42. Perkin, H. J., and Cattell, R. B.: Blood Iodine Levels Related to the Recurrence of Hyperthyroidism, Surg., Gynec. & Obst. **68**:744-748, 1939.

determinations of the iodine content of urine are mentioned. The daily excretion of iodine in the urine of a normal person may be influenced by the daily regimen, the district in which the person lives and physiologic sex factors. Scheffer [43] noted an increased urinary excretion of iodine in untreated patients with hyperthyroidism. From his studies Scheffer concluded that thyrotoxic patients had a negative iodine balance. Curtis and Phillips [44] concurred with this observation. Elmer and Schepps [32] reported that an increased excretion of iodine was present only in patients with severe hyperthyroidism. The problem has been studied more recently by Curtis and Puppel.[45] Because of the limited stores of iodine in the body, it is difficult to conceive of a patient with clinical hyperthyroidism having a negative iodine balance indefinitely. In this connection we [46] presented evidence to show that the blood iodine level was usually elevated in patients with clinical hyperthyroidism who had had symptoms of thyrotoxicosis for nine months or less; after the symptoms of hyperthyroidism had persisted untreated for one year or longer, the blood iodine was generally observed to be normal. This observation, together with the previously mentioned studies on the urinary excretion of iodine, is in keeping with the results of chemical and histologic studies which have shown decreased amounts of iodine and colloid in the thyroid glands removed from untreated patients with exophthalmic goiter.[47] Thus elevation of the blood iodine level and a concomitant increased urinary excretion of iodine would appear to be dependent on the presence and release of iodine from the thyroid gland. One might assume that the depletion of iodine from the thyroid gland of patients with exophthalmic goiter of long duration would result in spontaneous remission of the thyrotoxicosis. Although this is known to occur in some instances, we [46] have observed cases of severe, long-standing exophthalmic goiter in which no iodine was found in the blood and a negligible amount was excreted in the urine. The thyroid gland of such patients should be markedly deficient in iodine, but this fact could not be proved since iodine medication had

43. Scheffer, L.: Ueber die Jodbilann normaler Menschen, Biochem. Ztschr. **259**:11-18, 1933; Jodstoffwechsel bei Schilddrüsenkranken, Klin. Wchnschr. **12**: 1285-1286, 1933.

44. Curtis, G. M., and Phillips, F. J.: The Urinary Excretion of Iodine, J. Clin. Investigation **12**:963, 1933.

45. Curtis, G. M., and Puppel, I. D.: Increased Urinary Iodine in Hyperthyroidism, Arch. Int. Med. **60**:498-508 (Sept.) 1937.

46. Perkin, H. J., and Lahey, F. H.: Exophthalmic Goiter: Relation Between the Blood Iodine Level and the Duration of Symptoms in Three Hundred and Five Cases, Arch. Int. Med. **61**:875-879 (June) 1938.

47. Cattell, R. B.: The Pathology of Exophthalmic Goiter: Histologic and Chemical Changes Following Administration of Iodine, Boston M. & S. J. **192**: 989-996, 1925.

been given prior to subtotal thyroidectomy. The basis of thyrotoxicosis in hyperthyroid patients who are depleted of iodine requires further elucidation.

The amount of iodine appearing in the urine should be dependent on the concentration of diffusible iodine in the blood. The inorganic iodine of the blood is derived chiefly from iodides, from the intestinal tract and from the end products of the metabolism of organic iodine which has been synthesized and secreted by the thyroid gland. As early as 1900 Gley and Bourcet [5] dialyzed serum and found that most of the iodine present was nondiffusible. Since all the blood iodine was believed to be in the plasma or the serum, they concluded that it existed in protein combination. This was indeed an interesting observation for the time. Blum and Grützner [7] administered from 0.5 to 2 Gm. of sodium iodide to sheep and observed an increase of the iodine in the acetone extract of the blood. Veil and Sturm [10] fractionated the iodine of the blood by precipitating the blood proteins with alcohol. The fraction insoluble in alcohol was called the organic blood iodine. The results of these investigators showed that from 60 to 70 per cent of the total iodine in the blood of normal persons and of patients with exophthalmic goiter was in the organic blood iodine fraction. The aforementioned work lent credence to the idea of an actual hypersecretion of iodine from the thyroid gland in patients with thyrotoxicosis. Pincussen and Roman [48] employed a method of electrodialysis to remove the inorganic constituents from the blood. Barkam and Leistner [49] separated the iodine fractions in blood by precipitating the inorganic fraction with silver and nitric acid. They noted that the administration of potassuim iodide did not result in an increase in the organic iodine of the bood. Nuernbergk and Widmann [27] stated that the organic iodine in the blood was increased particularly in patients with exophthalmic goiter. Lunde, Closs and Pederson [50] used precipitation with alcohol followed by Soxhlet extraction to partition the iodine of the blood. They expressed the opinion that the nondiffusible iodine secured by their method constituted the active principle of the thyroid gland. They reported a relative decrease in the organic blood iodine following the oral administration of inorganic iodine in patients with hyperthyroidism; this decrease paralleled the decrease in the basal metabolic rate. Using similar methods of study,

48. Pincussen, L., and Roman, W.: Ueber den Einfluss der Bestrahlung auf die Fraktionen des Jods und Broms im Tierkörper, besonders nach Zufuhr von Jodsalzen, Biochem. Ztschr. **216**:336-361, 1929.

49. Barkam, G., and Leistner, W.: Das Verhalten des Jodes in den Körpersäften nach Verfütterung von Jodalkalien und Jodeiweiss, Klin. Wchnschr. **8**: 117-118, 1929.

50. Lunde, G.; Closs, K., and Pederson, O. C.: Untersuchungen über den Jodstoffwechsel, Biochem. Ztschr. **206**:261-274, 1929.

Dodds, Lawson and Robertson [51] were unable to confirm these observations. Nitzescu and Binder,[12] employing the fractionation method of Lunde and his associates,[50] reported the level of organic iodine in the blood to be relatively stable, with fluctuations occurring in the inorganic fraction. From a theoretic standpoint, estimation of the organic iodine in the blood should be a closer index of the amount of thyroid secretion than assumptions based on analyses of the total blood iodine. Such determinations should be of value for patients receiving iodine medication, provided that thyroid tissue alone has the capacity to synthesize organic iodine compounds. One of the present difficulties is lack of experimental proof that with the methods of fractionation all the iodine products in the so-called organic iodine fraction which may be secreted by the thyroid gland are recovered. This has been assumed by many investigators. In this connection Trevorrow's [52] studies on the nature of iodine in blood are of considerable interest. It has been our experience that methods of blood iodine fractionation involving precipitation with alcohol recover, in the so-called organic blood iodine fraction, organic compounds of a molecular weight of 7,000 and greater.[53] Thus thyroxine, if present in blood, would be recovered in the inorganic fraction. In contrast, when the principle of dialysis for partition of blood iodine was used, specific amounts of thyroxine, when added directly to samples of blood, were mostly withheld in the nondiffusible fractions.[54]

An increase in the level of organic blood iodine in all patients with thyrotoxicosis seems doubtful,[53] although one must recognize that a relative increase may occur when the total blood iodine is still within normal limits. No explanation can be offered for patients with clinical hyperthyroidism in whose blood no iodine can be demonstrated. In patients with thyrotoxicosis the average values for the organic blood iodine may show a relative decrease after iodine medication. The values are appreciably influenced by the amount and form of iodine administered and the time of analysis of blood iodine in relation to the previous dose of iodine. When the nature of iodine in the blood and the influence of iodine medication on the organic iodine components of blood are more clear, a definite understanding will be attained regarding the iodine metabolism in diseases of the thyroid.

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51. Dodds, E. C.; Lawson, W., and Robertson, J. D.: Variations in the Iodine Content of the Blood in Hyperthyroidism and Nontoxic Goiter, Lancet **2**:608-611, 1932.

52. Trevorrow, V.: Studies on the Nature of the Iodine in Blood, J. Biol. Chem. **127**:737-750, 1939.

53. Perkin, H. J., and Hurxthal, L. M.: The Fractionation of the Iodine of the Blood in Thyroid Disease, J. Clin. Investigation **18**:733-737, 1939.

54. Perkin, H. J.: Unpublished data.

Iodine medication in any form results in elevation of the level of iodine in the blood.[55] Veil and Sturm [10] noted that one and one-half hours after the oral administration of a single dose of iodine the maximum elevation in blood iodine occurred. Elmer [56] estimated the blood iodine level at specific intervals after the injection of 1,300 micrograms of iodine in the form of potassium iodide. From the results he noted a difference in the blood iodine curves which was apparently related to the degree of thyroid activity as determined clinically: A greater amount of iodine appeared in the blood of patients with hypothyroidism than in normal persons. This observation was attributed to the inability of the thyroid gland to remove the administered iodine from the blood. On this basis Elmer [56] proposed an iodine tolerance test as an aid in the clinical diagnosis of hypothyroidism. Perkin, Brown and Lang [38] and Perkin, Lahey and Cattell [39] reported a similar iodine tolerance test to facilitate in the diagnosis of clinical hyperthyroidism. The level of iodine in the blood was determined at intervals after the oral administration of 72 mg. of iodine (in the form of compound solution of iodine U. S. P.). We [57] later suggested that in so far as hyperplasia of the thyroid gland is associated with clinical hyperthyroidism this test ought to be of significance. More recently Watson [58] has added corroborative evidence to the aforementioned observations. We have concluded that the iodine tolerance test is of more scientific interest than practical value. The blood iodine curves secured from patients are often irregular and difficult to interpret. This may be due to factors other than thyroid tissue affecting the blood iodine level during iodine medication.[59] However, the iodine tolerance test may still be used to advantage in isolated cases.

It seems pertinent to mention that certain factors other than the thyroid gland may produce alterations in the level of iodine in the blood. As these factors may play a role in the cause or in the effects of thyroid disease, they should be recognized by those interested in the

55. Perkin, H. J., and Cattell, R. B.: The Practicability and Significance of Blood Iodine Estimations, New York State J. Med. **36**:1033-1035, 1936.

56. Elmer, A. W.: Iodine Tolerance Test for Thyroid Insufficiency, Endocrinology **18**:487-496, 1934.

57. Perkin, H. J., and Lahey, F. H.: The Iodine Tolerance Test as an Aid in the Diagnosis of Clinical Hyperthyroidism, New England J. Med. **216**:501-503, 1937.

58. Watson, E. M.: An Iodine Tolerance Test for the Investigation of Thyroid Function, Endocrinology **20**:358-362, 1936; The Relation of the Iodine Tolerance to Thyroid Function, ibid. **22**:528-537, 1938.

59. Perkin, H. J., and Brown, B. R.: The Influence of the Thyroid Gland and of the Ovary on the Metabolism of Iodine: Experimental Study in Dogs, Endocrinology **22**:538-542, 1938.

biochemistry of iodine in goitrous conditions. Iodine in the diet in unsuspected forms (such as in sea food and iodized salt) affect the blood iodine level.[58] Excessive amounts of calcium in the diet affect the blood iodine level in experimental animals [60] and may also exert an influence in human beings. Iodine medication (administration of compound solution of iodine U. S. P. orally, iodides intravenously, iodine preparations cutaneously or roentgen ray dyes orally or intravenously [61]) within one month prior to the analysis of blood iodine may result in an abnormal value. Elevation of blood iodine may be found in patients with diseases of the liver and of the biliary passages.[62] In leukemia [13] and in the early stages of acromegaly [54] there usually occurs an elevation in the level of iodine in the blood. Most anesthetics [63] and all surgical procedures [35] result in an immediate increase in the blood iodine. Strenuous exercise may increase the blood iodine slightly,[35] while complete rest usually causes it to fall. As previously noted, variations in the level of iodine in the blood may be observed in women during the menstrual cycle and during pregnancy. These variations in the level of blood iodine may or may not extend beyond the normal range for the method used. One should bear in mind that a value at the upper normal limit may actually be an elevation of blood iodine for the particular person.

Analyses of blood iodine were made on 1,823 persons. In 745 persons who presented no clinical evidence of thyrotoxicosis (chart) the average (or mean) level of iodine in the blood was 6.8 micrograms per hundred grams. The values for blood iodine ranged from 2 to 15 micrograms per hundred grams of blood, with 61 persons (8.2 per cent) having a value in excess of the upper normal limit by the method (10 micrograms per hundred grams). The results showed no significant variations attributable to age, sex or season. It was found generally that normal persons of a vagotonic type had blood iodine values within the lower normal range. On the other hand, normal persons of a sympathicotonic type were found usually to have blood iodine values within the upper normal range. Since the same person varies in temperament, the level of iodine in the blood may fluctuate in a similar manner. The correlation, however, could not be considered absolute.

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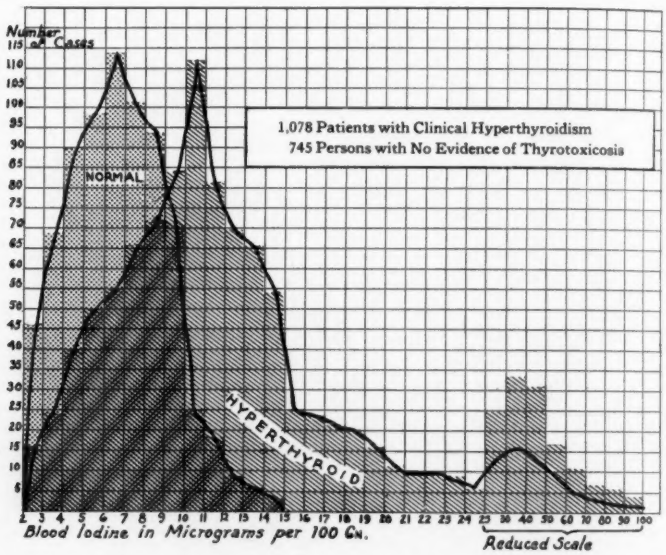
60. Thompson, J.: Influence of the Intake of Calcium on the Blood Iodine, Endocrinology **20**:809-815, 1936.

61. Perkin and Cattell.[55] Elmer.[56] Veil and Sturm.[10]

62. DeCourcy, J. L.: Iodine Metabolism, Normal and Abnormal: Its Relation to the Reticulo-Endothelio System, Tr. Am. A. Study Goiter, 1937, pp. 133-139. Perkin and Cattell.[55]

63. Anderson, W., and Leitch, I.: Effect of Anaesthetics on the Blood Iodine, Lancet **2**:1391-1392, 1927.

The blood iodine values for 1,078 patients with clinical hyperthyroidism [64] are also shown. The average value for blood iodine was 15.5 micrograms per hundred grams. The mean level was considerably less, 11 micrograms per hundred grams. The range was from 2 to 100 micrograms per hundred grams. Approximately 34 per cent of the patients had blood iodine values of less than 10 micrograms per hundred grams. As previously pointed out, the presence in a specific case of an elevated or normal blood iodine value was roughly dependent on the duration of the hyperthyroid syndrome. Although the level of iodine in



Results of blood iodine analyses in 1,823 persons.

the blood of patients with thyrotoxicosis may be influenced by states of excitement or of rest, the degree of variation was not as great as in normal persons. The ages of the patients under consideration ranged from 3 to 80 years, with no difference apparent in the effect of hyperthyroidism on the level of iodine in the blood.

In a review of the short history of investigations on the quantitative determination of iodine in blood, it is of interest that there has been a gradual decrease in the so-called normal blood iodine level. This transition reflects improvements in technical procedures together with a

64. No case in which iodine medication had been given within three months prior to examination was included.

better understanding of the sources of error in the methods for the microestimation of iodine. The development has been complemented by the availability of improved (iodine-free) chemicals. Baumann and Metzger [65] have pointed out that many of the earlier results of the estimation of iodine in the blood are too high. The ideas presented suggest the difficulty in determining the absolute amount of iodine in blood. However, the fact is not precluded that the results of determinations of iodine in the blood of different patients or of the same patient at different times are not relative one to another when estimated by the same method and by a worker familiar with the method. The relative blood iodine values have added considerably to the present conception of iodine metabolism in goitrous conditions.

65. Baumann, E. J., and Metzger, N.: On the Amount of Iodine in Blood, J. Biol. Chem. **121**: 231-234, 1937.

USE OF ALPHA LOBELINE FOR MEASUREMENT OF VELOCITY OF BLOOD FLOW

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Various methods for the measurement of the velocity of blood flow are now commonly employed. Most of them are subjective—they depend for their results on the cooperation of the patient; therefore, they not infrequently yield inaccurate results or fail altogether. The objective methods hitherto employed either are too complicated for ordinary clinical use or are potentially harmful to the patient. Recently the Russian authors Teplov and Sor [1] have suggested the use of alpha lobeline as an agent for the measurement of the velocity of blood flow. To my knowledge, this new, objective method for estimating "circulation time" has not yet been used in this country. I have undertaken, therefore, to investigate its merits, and I present the following preliminary report.

DESCRIPTION OF TEST

Technic.—Prior to the test the patient is kept in a reclining position for about ten minutes. No preliminary instructions are given, and any remarks which might indicate the expected reaction are carefully avoided. Five milligrams of alpha lobeline hydrochloride (0.5 cc. of the 1 per cent solution [2]) is rapidly injected into an antecubital vein. Several seconds later the patient experiences a choking sensation in his throat, comparable to that produced by the sudden inhalation of smoke. Usually this is accompanied by a grimace or a sudden start. Immediately thereafter the patient coughs. Hyperpnea may precede or follow the cough and may continue for one or two minutes. The time interval from the beginning of the injection to the onset of coughing, measured by a stopwatch, represents the "circulation time" for the patient. If cough fails to appear, the test is repeated with 7.5 mg. of alpha lobeline hydrochloride ten to fifteen minutes later.

Principle of the Test.—All methods for determining circulation time measure the time between the intravenous injection of an agent at one

From the Cardiological Department of Sydenham Hospital.

1. Teplov, I., and Sor, V. G.: Graphic Method for Determining the Velocity of Blood Circulation by Means of Lobeline, Terap. ark. **13** (no. 2):57-80, 1935.

2. The ampules of alpha lobeline hydrochloride used in this study were supplied by the Sandoz Company.

point and the perception of its effect at another point, the point of arrival. In the lobeline test, the latter point is the carotid sinus.[2a] Lobeline has long been known to stimulate the respiratory center (Sollmann [3]) and thus to produce hyperpnea and cough. Recently, however, Heymans, Boukaert and Dautrebande,[4] in experiments on animals, found that lobeline does not stimulate the respiratory center directly but that it acts on the carotid sinus, from which the respiratory center is stimulated by reflex action. "Lobeline circulation time," therefore, is "arm to carotid circulation time." To reach the carotid sinus, the injected lobeline travels from the antecubital vein by way of the subclavian vein, right side of the heart, lesser circulation, left side of the heart, aorta and carotid artery.

RESULTS

Two hundred and eighteen tests were made on 162 patients. In 151 patients (93 per cent) the circulation time was successfully determined by one or more tests. In 11 patients (7 per cent) the test failed to give the circulation time. Only 5 of these 11 had more than one injection; the remaining 6 were not available for repetition of the test. Had they been available, the percentage of failures would certainly have become less than 7 per cent.

Different amounts of alpha lobeline hydrochloride were used (table 1); 115 patients each received 5 mg. In 87 of these (76 per cent) the test was successful at the first attempt; in 28 (24 per cent) it failed. Of these 28 persons, 24 were available for repetition of the test. This was done, using 7.5 mg. of the drug in 11 instances (8 successes, 3 failures) and 10 mg. in 13 instances (10 successes, 3 failures). A second group of 58 patients, including the 11 just mentioned in whom the test with 5 mg. had failed, each received 7.5 mg. In 46 patients (79 per cent) the test was successful; in 12 (21 per cent) it failed. Furthermore, 16 persons were given a test with 10 mg., after smaller doses had failed, and in 10 of the 16 the circulation time was then obtained. Only 11 patients were given 11 to 13 mg. after smaller doses had failed, and in 8 of these the circulation time was at last obtained.

The 162 patients varied in age from 14 to 75; 82 were men and 80 were women. Of the 151 patients for whom circulation time was obtained, 33 were free from demonstrable cardiac disease; their circu-

2a. An additional site of attack of alpha lobeline, perhaps in the bronchial wall, may exist. This possibility is suggested by the fact that very low figures for circulation time (five seconds) are occasionally obtained with this test.

3. Sollmann, T.: A Manual of Pharmacology, ed. 4, Philadelphia, W. B. Saunders Company, 1932, p. 424.

4. Heymans, C.; Boukaert, J. J., and Dautrebande, L.: Sinus carotidiens et actions stimulantes respiratories de la nicotine et de la lobeline, Compt. rend. Soc. de biol. **106**:469, 1931; **109**:56, 1932.

lation time varied from five to twelve and one-half seconds, with an average of eight and one-half seconds. Seventy patients were suffering from various types of heart disease but did not show any signs of cardiac failure; their circulation time varied from seven to eighteen seconds, with an average of ten seconds. Lastly, 43 patients were suffering from cardiac disease with congestive heart failure; their circulation time varied from seven to forty-six seconds, with an average of nineteen seconds. These results are summarized in table 2. With few exceptions, the results of the lobeline test corresponded quite well to the clinical estimations of the degree of cardiac failure. However, detailed comparisons have been deferred until a time when a larger number of patients will have been tested.

TABLE 1.—*Effectiveness of Various Doses of Alpha Lobeline*

	Amount of Alpha Lobeline Hydrochloride			
	5 Mg.	7.5 Mg.	10 Mg.	11 to 13 Mg.
Total number of tests	115	58	16	11
Successful tests	87 (76%)	46 (79%)	10	8
Failures	28 (24%)	12 (21%)	6	3

TABLE 2.—*Relation of Alpha Lobeline Circulation Time to Cardiac Disease*

	No Cardiac Disease	Cardiac Disease Without Signs of Congestive Failure	Cardiac Disease With Signs of Congestive Failure
Total number of patients	35	78	49
Number of patients in whom circulation time was obtained	33	74	44
Average circulation time	8½ sec.	10 sec.	19 sec.

COMMENT

Teplov and Sor [1] suggested the use of 0.03 to 0.04 mg. of alpha lobeline per kilogram of body weight of the patient. Their usual dose, therefore, was less than 3 mg. They made 300 tests on 165 persons and produced cough in 60 to 70 per cent. I began by using 3 mg. doses for a series of 37 patients, not included in the present study, and as a result I had 15 failures (41 per cent). It soon became apparent that body weight was only a minor factor in determining the amount of alpha lobeline necessary to produce cough. Age, sex and, especially, individual variations in nervous irritability appeared to be much greater factors than weight. Women reacted more markedly than men and required smaller doses. Young persons required smaller amounts than old persons. Apprehensive persons responded to smaller amounts than did quiet, well controlled persons.

These conclusions from my experiences were supported by an analysis of those instances in which the test failed completely. If weight were the most important factor, the majority of these patients should have been heavy. Instead, of the 9 patients in whom doses of 10 to 12 mg. of alpha lobeline failed to produce cough, none were stout; the heaviest weighed 158 pounds and the lightest, 138. All 9 were men. Only 1 of them (his age was 38) was below 40 years of age; 3 were above 60 years of age.

Demonstrable impairment of cerebral function seemed to inhibit somewhat the action of alpha lobeline. Only 4 patients who were in comatose or stuporous states were included in this series. All of these patients required larger doses, 7.5 to 12 mg. The results obtained on these 4 patients were, on the average, higher than those obtained on the remaining patients. A separate investigation is under way to determine how impairment of cerebral function by disease or by drugs affects the result of the lobeline test.

Untoward Reactions.[5]—None of the 218 tests resulted in any injury to the patient. There were, however, certain unpleasant by-effects. The majority of the patients merely complained of a mild choking sensation, "as if fumes had gotten into the throat." Sometimes a patient gave a sudden start several seconds after the injection, put a hand to the throat as if to seek relief from a constriction and then coughed more or less violently a few seconds later. Other patients merely swallowed visibly or grimaced slightly before the cough began. One or two later spoke of having experienced a strangling sensation. In several instances, especially when 7.5 mg. was used without a previous test with 5 mg., the patient was considerably frightened by the sensation in the throat. On the other hand, many patients experienced no choking sensation whatsoever, and in the majority of patients it was so slight as not to frighten them. A few patients later stated that they had felt "light headed" or "faint."

The cough produced by alpha lobeline, which followed these various subjective sensations and which represents the real end-point of the test, varied from one clearing of the throat to a rather violent spell of coughing lasting two or three minutes. In 2 instances, again when 7.5 mg. was injected without trial of a smaller dose first, the patient presented the picture of severe bronchospasm. These spells distressed and frightened the patients markedly, but fortunately were of short duration.

5. Stanojevic, L.: Die Bestimmung der Kreislaufzeit mit Lobelin, Ztschr. f. Kreislaufforsch. **30**:521, 1938. Evzlina, M. M.: Lobeline in Determination of Velocity of Blood Circulation, Vrach. delo **20**:113, 1938. Trimarchi, E.: Sul metodo della lobelina per la misura della velocità circolatoria, Riforma med. **54**: 1407, 1938. Arrillaga, F. C., and de Soldati, L.: Determinación objetiva de la velocidad circulatoria por la lobelina, Semana méd. **1**:453, 1939.

The occasional occurrence of such excessive effects of lobeline undoubtedly constitutes the chief disadvantage of the method. They seem, however, to be avoidable by proper regulation of the dose. Most of the unpleasant reactions were observed at the beginning of this work, when I used larger doses. I have since learned to vary the dose according to the age, sex and individual irritability of the patient. While 5 mg. was the amount I injected in the majority of experiments reported here, 3 mg. seems a safer initial dose; it is certainly to be recommended for all persons below 25 years of age, especially women, and also for all adults over 25 years who appear apprehensive or excitable. Whenever a patient must be kept at complete rest (as, for example, after myocardial infarction), the smaller dose, of 3 mg., is also indicated. In all such instances, rather than produce an unpleasant reaction, I prefer to risk initial failure and if necessary to repeat the test, with a larger dose. Patients who failed to cough after the first injection never had a violent reaction to a second, larger dose. The best safeguard against such reactions, therefore, is the use of a smaller amount of alpha lobeline at the start.

None of the 218 injections had any irritating local effect; venous thrombosis, in particular, was never seen after an injection.

Possibility of Error.—At first I was tempted to consider as end-points sudden movements of the patient's throat, grimacing and other indirect signs of the effect of alpha lobeline which occur earlier than cough or which may occur in the absence of cough. I soon gave up that practice, since it made the end-point subject to individual interpretation. A sharp, easily perceptible end-point is necessary if circulation time is to be measured with any degree of accuracy. Cough, or rather the onset of cough, represents such an end-point. Repetition of the test on the same patient proved the reliability of this technic by yielding the same result each time. Only once did the reliance on cough lead to an error: The patient coughed accidentally five seconds after the beginning of the injection, and a wrong time was obtained.

Another possibility of error may arise from the fact that the figures for circulation time will vary in the same patient if the amounts of alpha lobeline are varied. Larger amounts of the drug usually result in slightly lower figures for circulation time. Eight patients were given two successful tests on the same day, one with 5 mg. and the second with 7.5 mg. In 6 of the 8 experiments the second test yielded a lower figure for circulation time. The differences ranged from one-half second to seven seconds. Therefore, whenever tests are repeated for comparison, it is necessary to use exactly the same dose of lobeline each time. I found it practical always to record in the chart the amount of alpha lobeline used, together with the result of the test; for example, "Lobeline circulation time 9 seconds (5 mg. used)."

Contraindications.—So far I have found only one definite contraindication to the use of the alpha lobeline test, namely, recent hemoptysis. On a patient suffering from mitral stenosis who presumably had had pulmonary infarction, the test was made inadvertently. Hemoptysis, which had ceased only the day before, promptly started again. Other possible contraindications, such as bronchial asthma or acute inflammatory conditions of the lung, may be found by future observation. Dyspnea per se, I found, is not a contraindication; some dyspneic patients stated that they actually felt better shortly after the test.

ADVANTAGES AND DISADVANTAGES

Advantages and disadvantages of the alpha lobeline test to determine circulation time may be briefly enumerated:

Advantages

1. The method is simple.
2. The result does not depend on the willingness or ability of the patient to cooperate.
3. The end-point, cough, is sharp and readily perceptible.
4. No injurious effect, either local (venous thrombosis) or systemic, has been noted.
5. Only a small amount of material, 0.5 cc., is required; the duration of the injection, therefore, is short.
6. Lobeline has no cumulative effect; the test may be repeated after fifteen minutes.

Disadvantages

1. There is a possibility of unpleasant reactions (choking sensation, excessive cough, fright).
2. It is frequently necessary to repeat the test because the initial dose has been too small.
3. Complete failure may occur.
4. Results vary slightly with the amount of alpha lobeline used.
5. Results possibly may be influenced by processes of cerebral origin —for example, coma.

CONCLUSIONS

1. The alpha lobeline test is a practical method for the measurement of the velocity of blood flow.
2. Age, sex and individual variations in nervous irritability are major factors in determining the minimum amount of alpha lobeline required to produce cough; body weight is only a minor factor.

RETICULOENDOTHELIAL CYTOMYCOSIS

(HISTOPLASMOSIS OF DARLING)

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A fatal disease so rare that in the third of a century following the original description only 4 cases of it were reported should merit only a passing or academic interest. However, when 5 other cases of the disease, which is a definite clinical entity, appear in southern Michigan in the course of a few months a new diagnostic problem is unquestionably thrust on physicians.

Darling,[1] in 1906, was the first to note in smears and sections taken at autopsy from the viscera of a Negro who had died at the Ancon Hospital in the Canal Zone a peculiar coccus-like organism which packed the endothelial cells. In the ten months after the first case he observed the same histologic picture in the cases of 2 other residents of Panama.[2] Clinically, the syndrome (splenomegaly, irregular pyrexia and leukopenia) resembled that of kala-azar, and the microscopic appearance was so similar to that of kala-azar that, although he found no typical Leishman-Donovan bodies, Darling felt that the new organism must be protozoan in character; he therefore called it Histoplasma capsulatum [3] and applied the name "histoplasmosis" or "reticuloendothelial histoplasmosis" to the disease. In 1934, however, De Monbreun [4] demonstrated that a fungus was the etiologic factor, and, since the old term was misleading, he suggested the name "cytomycosis" for the disease. For the sake of pathologic description, although with some sacrifice to brevity, I would retain the prefacing "reticuloendothelial," for the reticuloendothelial system, almost alone, is the portion of the body involved.

From the Leila Y. Post Montgomery Hospital Laboratory.

1. Darling, S. T.: A Protozoön General Infection Producing Pseudotubercles in the Lungs and Focal Necroses in the Liver, Spleen and Lymphnodes, J. A. M. A. **46**:1283 (April 28) 1906.

2. Darling, S. T.: Histoplasmosis: A Fatal Infectious Disease Resembling Kala-Azar Found Among the Natives of Tropical America, Arch. Int. Med. **2**: 107 (Sept.) 1908.

3. Darling, S. T.: The Morphology of the Parasite (Histoplasma Capsulatum) and the Lesions of Histoplasmosis, a Fatal Disease of Tropical America, J. Exper. Med. **11**:515, 1909.

4. De Monbreun, W. A.: The Cultivation and Cultural Characteristics of Darling's Histoplasma Capsulatum, Am. J. Trop. Med. **14**:93 (March) 1934.

After Darling's reports, no further cases of what was considered a rare tropical disease were noted until 1926, when Watson and Riley [5] reported the case of a woman who had been a resident of Minnesota for over forty years. In the same year Phelps and Mallory [6] described a case in Honduras, and in 1931 a second case in the United States was described.[7] In 1934 Dodd and Tompkins [8] reported the first case in which diagnosis was made during life, on the basis of blood smears. This was the case of an infant in Tennessee. The first cultural studies of the organism were made in this case by De Monbreun.[4] These workers found that it was possible to observe the organisms in blood smears prepared with Wright's stain but that supravital preparations stained with neutral red were much superior.

Recently 5 cases of the disease have been observed in a limited area in Michigan. Amolsch,[9] in Detroit, has described 1; 2 have been noted in the department of pathology at the University of Michigan [10] (the characteristic organisms were seen only in an adrenal and a lymph gland, respectively) and I have performed necropsies in 2 cases within twenty-five miles of Battle Creek. Oddly, the autopsies in these last 2 cases were performed but forty-eight hours apart.

REPORT OF CASES

CASE 1 (Patient of Dr. A. B. Gwinn, Hastings, Mich.).—S. R., a white youth aged 17, was admitted to the Pennock Hospital on Aug. 23, 1937, because of a persistent infection of the upper respiratory tract which in the few days prior to entry had developed into pneumonia. His condition was not considered serious, and he immediately started to improve; but he remained in the hospital because a profound leukopenia was discovered during the routine laboratory examination.

His health had been excellent prior to the present illness, with the exception of a fungous infection in one ear in 1935. He had been born and had lived in northern Indiana until he was 1½ years of age; since that time he had lived in a small city in central Michigan. There was no history of suspicious medication which might have depressed the production of leukocytes.

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5. Riley, W., and Watson, C. J.: Histoplasmosis of Darling: Report of a Case Originating in Minnesota, Am. J. Trop. Med. **6**:271 (July) 1926. Watson, C. J., and Riley, W. A.: A Case of Darling's Histoplasmosis Originating in Minnesota, Arch. Path. **1**:662 (April) 1926.

6. Phelps, B. M., and Mallory, F. B.: Toxic Cirrhosis and Primary Liver Cell Carcinoma Complicated by Histoplasmosis of the Lung, in Fifteenth Annual Report of the Medical Department of the United Fruit Company, New York, United Fruit Company, 1926, p. 115.

7. Crumrine, R. M., and Kessel, J. F.: Histoplasmosis (Darling) Without Splenomegaly, Am. J. Trop. Med. **11**:435 (Nov.) 1931.

8. Dodd, K., and Tompkins, E. H.: A Case of Histoplasmosis of Darling in an Infant, Am. J. Trop. Med. **14**:127 (March) 1934.

9. Amolsch, A. L., and Wax, J. H.: Histoplasmosis in Infancy, Am. J. Path. **15**:477 (July) 1939.

10. Parsons, R. J.: Personal communication to the author.

On the day of admission the physical findings, with the exception of those associated with the mild pneumonia, were essentially negative. The hemoglobin content of the blood was 70 per cent (Sahli); there were 3,750,000 erythrocytes per cubic millimeter of blood and 1,900 leukocytes, of which 31 per cent were polymorphonuclear neutrophils and 69 per cent were lymphocytes. Later in the day the count was repeated and 1,600 leukocytes were found, with only 25 per cent polymorphonuclear cells. Urinalysis gave negative results.

Course.—Pentnucleotide (30 cc.) was given on the following day, and, although the leukocyte count did not increase, the percentage of granulocytes increased to 30. Over a period of eight days an additional 120 cc. of pentnucleotide was given, and the white blood cell count rose slowly but steadily to 3,200, with approximately 40 per cent polymorphonuclear neutrophils on Sept. 3, 1937. Treatment was then discontinued. The patient left the hospital on October 16, apparently in good health; the leukocytes numbered 4,500, and although the percentage of polymorphonuclears had previously reached a peak of 65, it was then 40, with 60 per cent lymphocytes.

The patient renewed his former life and graduated from high school in June 1938. On July 8 he was readmitted, a number of bullous lesions having appeared on his face and body. Stomatitis developed, from which Vincent's organisms were recovered. These lesions subsided after five days of sulfanilamide therapy. A blood count was made on July 8 which showed a hemoglobin content of 105 per cent, a red cell count of 5,000,000 and 4,000 leukocytes, of which 90 per cent were lymphocytes and 10 per cent were polymorphonuclear neutrophils.

Some ulceration of the roof of the mouth still existed when he was examined on August 29 by Dr. John D. Littig, and there were large masses of palpable glands, which appeared to be matted together on each side of the neck. Some involuted erythematous patches were still present on the face, and a small gland was palpable in the left axilla. The liver and spleen were not palpable. The temperature was 103 F. and the pulse rate 105. He had severe anemia, with a hemoglobin content of 40 per cent (5.6 Gm.) and a red cell count of 1,600,000. His leukocyte count was 3,150, with a differential count of 54 per cent small lymphocytes, 46 per cent large lymphocytes, one megaloblast and many normoblasts. The Kahn and heterophile tests were negative.

During the next six weeks he was given seven blood transfusions (500 cc. each) and placed on a high caloric diet, with vitamin C and yellow bone marrow. Pentnucleotide was given twice daily until thirty-eight injections had been given. About October 1 his fever subsided; he was discharged from the hospital and was up and about at home. On October 5 it was found that his lymphadenopathy had disappeared. He complained of dysphagia and hoarseness, had lost 20 pounds (9 Kg.) in weight and felt very weak. There were no physical findings of note at this time, and the liver and spleen were not palpable. The hemoglobin content was 64 per cent and the red blood cell count 3,400,000. The leukocytes numbered 2,700; one week later they fell to 2,075 with 18 per cent polymorphonuclears, 75 per cent lymphocytes and 7 per cent eosinophils in the differential count. The platelets, as in previous counts, appeared to be normal. On December 5 the leukocyte count reached 5,800, but the granulocytes varied between 3 and 30 per cent and the patient was obviously failing.

On Jan. 9, 1939 the leukocytes had dropped to 1,500, with only 15 per cent polymorphonuclears. Roentgen therapy was then given over the long bones for three periods, with very obvious clinical improvement; and while the white blood cell count remained near 2,000, the percentage of polymorphonuclears increased to 55 by February 5. The patient was up and about at this time, but the anemia

again became marked, and purpura developed. On March 8 he was given two transfusions in the home. On the following morning he experienced a sudden loss of vision, lapsed into a coma and died within a few hours. A few days prior to death it had been believed that the liver was palpable but that the presence of what appeared to be ascites prevented definite assurance.

Necropsy (March 10, 1939).—The body was emaciated but well developed. The heart was slightly enlarged and lay free in a sac containing approximately 80 cc. of clear straw-colored fluid. There were some firm white nodules, which measured between 3 and 6 mm. in diameter, on the anterior surface of the left ventricle. A similar nodule, 2 mm. in diameter, was also present on one of the papillary muscles in the interior of the ventricle; this nodule had a faint yellow tint. The pleural cavities contained small amounts of slightly cloudy fluid. The left lung was firmly adherent to the parietal pleura. The visceral pleurae of both lungs were dotted with small white nodules which were slightly raised or appeared as flat plaques. The surface of the liver showed nodules of the same type, which varied from pinhead size to 1 cm. in diameter, and a few were scattered through the interior of the liver; on cross section they were white and were vaguely demarcated. The liver was enlarged 50 per cent and was yellowish brown in color. The spleen weighed approximately 700 Gm., small white plaques and nodules were scattered over its surface and on cross section it appeared dark red, with occasional small nodules of white on a firm smooth surface. There was about 400 cc. of clear straw-colored fluid in the peritoneal cavity. With the exception of a few of the small white nodules on the peritoneal surface of the pylorus and duodenum, the gastrointestinal tract was essentially normal. The lymph nodes of the mesentery were enlarged, and a huge mass of lymph nodes, matted together, buoyed up the pancreas. On cross section, these nodes were yellowish and somewhat necrotic in certain areas. The adrenals were autolyzed. The kidneys were enlarged (30 per cent) and pale, and their capsules stripped readily.

Microscopic Study.—Sections through the pleural nodules and through those from the interior of the lung showed masses of endothelial macrophages filled with small, coccus-like, dark-staining bodies with white halos or capsules about them. There were but a few in some cells, and they were densely packed in others. In some nodules there was marked central fibrosis and in others necrosis; in either event the periphery was dotted with intact or degenerating histiocytes filled with the organisms. In other nodules, where fibrosis was marked, there was no necrosis and few organisms were present. There was a marked infiltration of lymphocytes and plasma cells in this type of nodule, but in the other types there appeared to be no leukocytic reaction or response.

In the spleen packed histiocytes of the same type were scattered about; some of them were free in the sinuses. There were extensive areas of necrosis about some of the larger vessels, with many organism-packed cells in their outer zones.

Collections of the involved histiocytes were scattered more or less uniformly throughout the liver; some areas showed necrosis and a mild fibrosis. The hepatic cells contained a moderate amount of fat and some brown pigment granules and were somewhat distorted. Almost all of the Kupffer cells were involved and, although in many instances they were quite isolated from the large cell collections, were filled with the organisms.

In the cardiac musculature there were several large areas in which there were cells packed with organisms, numerous plasma cells and what appeared to be immature lymphocytes. These areas were often so extensive as to cover a

low power field. In the renal tubules, with the exception of some granular degeneration, there was little change. In about a third of the glomeruli, however, one or more cryptococcus-filled histiocytes were observed in the tufts (fig. 1). Sections through the lymph glands showed marked necrosis, but few organisms were present. The infiltration of plasma cells and lymphocytes was most pronounced in these enlarged nodes. Sections through the pancreas showed an occasional organism-filled cell in the interstitial tissue, and many lymphocytes. Sections through the intestinal wall showed nothing of note.

Diagnosis.—The diagnosis was reticuloendothelial histoplasmosis of Darling.

CASE 2 (Patient of Dr. D. B. Morrison, Tekonsha, Mich.).—H. S., a white man aged 46, was admitted to the Leila Y. Post Montgomery Hospital on Feb. 7, 1939. He complained of anorexia and weakness, which had become progressively worse

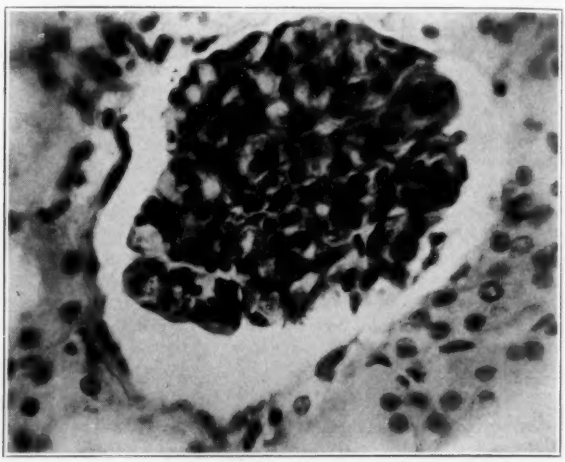

Fig. 1.—Glomerulus; four organism-filled cells enmeshed in the capillary tuft. × 300.

since their onset in September 1938. In the previous three months he had lost 30 pounds (13.5 Kg.). Since the last of December he had had several severe chills associated with bouts of fever and profuse sweats. Recently he had been nauseated and had vomited frequently. He had been forced to discontinue his farm work, although he experienced no pain and was perfectly comfortable if he remained in bed. Recently there had also been some postprandial abdominal pain.

The patient had always lived and worked on a farm in Michigan. His past history was one of long-standing poor health. He had suffered from colitis since childhood and had had an appendectomy in 1927. In 1919 a dog bite required several stitches, and the year following he had had a severe infection in one foot following a penetrating wound from a sharp stick. His father died from nephritis; the remainder of the family history was essentially irrelevant.

Physical examination revealed an emaciated man who weighed 110 pounds (49.5 Kg.) and was 5 feet 6 inches (168 cm.) in height. He presented the picture of a chronic invalid; the slightest exertion required obvious effort. The liver could

be palpated and had a smooth border extending slightly below the costal margin. At this time the spleen appeared to extend almost to the iliac crest, yet a few days later it could scarcely be palpated. No tenderness was present. The blood pressure was 120 systolic and 80 diastolic. He was deaf in the left ear.

A blood count on January 23 had revealed a hemoglobin content of 78 per cent, an erythrocyte count of 4,360,000 and a leukocyte count of 6,200. A differential count showed 44 per cent polymorphonuclear neutrophils, 43 per cent lymphocytes, 7 per cent eosinophils, 3 per cent monocytes and 3 per cent "stab" cells. On his entry into the hospital the hemoglobin reading (photelometer) was 58 per cent. The red cell count was 3,380,000 and the white cell count 6,450, of which 64 per cent were polymorphonuclears, 24 per cent lymphocytes, 2 per cent monocytes and 8 per cent myelocytes. Smears showed marked polychromasia and anisocytosis and several megaloblasts and normoblasts. The Kahn, Widal and undulant fever agglutination tests were negative. A fractional gastric analysis revealed only a small amount of combined acid until after the first hour, when, after histamine, the free acid reached 12 degrees. Urinalysis gave negative results. Roentgen examination on February 8 demonstrated a normal stomach and duodenum. The hili of the lungs were thickened, and there was some mottling in the lower pulmonary fields. Some enlargement of the liver and spleen was noted.

Course.—From Jan. 22, 1939, when his case was first recorded, until his death, on March 10, 1939, his temperature varied between 102 and 105 F. in the afternoons and returned to normal in the evening.

During the five day stay in the hospital the temperature "spiked" between 102.2 and 104 F. The night sweats were drenching. Splenic puncture was attempted but was abandoned in accordance with the patient's wishes. Treatment consisted of four blood transfusions and solution of potassium arsenite U. S. P. He left the hospital unimproved on February 12. At home he became progressively weaker and more irrational, and he died on March 10.

Necropsy (March 11, 1939).—The embalmed body was emaciated. When the thoracic cavity was opened, a small amount of clear fluid was found in the left pleural cavity. The right lung was firmly adherent to the chest wall. In the apex of the left lung there were a number of nodules, gray or white in color and firm on cross section, the largest of which measured 8 mm. in diameter. There was, however, one spongy, dark reddish brown nodule, which measured 9 or 10 mm. in diameter. There were some calcified hilar nodules, and the lower lobes of both lungs were dark, heavy and noncrepitant. On cross section, there were noted an increase in fluid and a markedly decreased froth. The heart appeared normal.

Examination of the abdomen showed the liver to be normal in color and slightly enlarged; it was normal on section. The spleen was enormously enlarged (600 Gm.) and on cross section was dark red, with a smooth, even surface.

The gastrointestinal tract appeared to be normal, as did the gallbladder, adrenals and pancreas. The kidneys were normal in size but were bound together at the lower poles by a fibrous band 5 mm. thick and 2 cm. wide. The ureters arose from the lower poles of the kidneys and, with the pelves, lay far anterior to their usual position. The bladder and prostate were normal. The testes were small and on cross section did not "string."

Microscopic Study.—Sections through the liver showed collections of histiocytes filled with cryptococci; numerous isolated reticuloendothelial cells were also involved (fig. 2). There was very little necrosis, and the liver cells, except for a small amount of fat in certain areas, appeared essentially normal. There were a few scattered lymphocytes but no polymorphonuclear cells.

Splenic sections showed areas of necrosis ringed about by the filled histiocytes. There was some fibrosis, and a few plasma cells and lymphocytes were present. There were some cells of the Sternberg type—small and with three or four superimposed nuclei centrally located in a dark cytoplasm. There were a few isolated cells filled with the coccus-like organism.

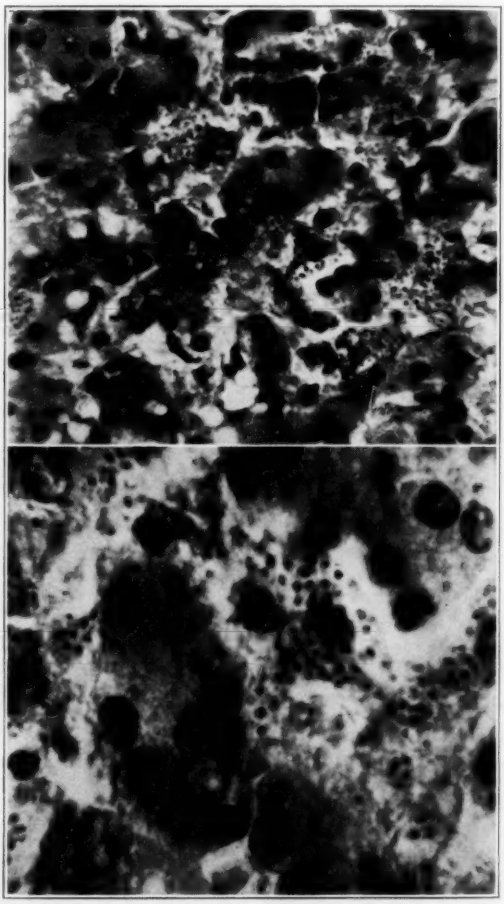

Fig. 2.—Sections of liver; histiocytes packed with the organism. × 300; × 800.

Sections through the kidney showed some tubular atrophy and an increase in connective tissue. There were some fibrous hyalinized crescents about the glomeruli, and some of the tufts showed one to a dozen isolated phagocytic cells filled with the organisms.

The glands removed from the hilus of the lung showed a typical healed tuberculous process; those from the abdomen, although not enlarged, showed the organism-packed histiocytes and the multinucleated cells with a large number of plasma cells.

The small white nodules in the lung resembled those found in case 1; but the solitary brown nodule was a cavity filled with a tangle of mycelial strands (fig. 3). There were no coccoid forms in or about it.

No organisms were observed in sections of the heart or prostate.

Diagnosis.—The diagnosis was reticuloendothelial histoplasmosis of Darling; horseshoe kidney; bronchopneumonia; healed pulmonary tuberculosis.

Comment on the Histologic Observations.—While it may appear from the foregoing descriptions that the histologic sections in these cases resemble each other closely they actually do not. In the first case a more general involvement was apparent even in microscopic section, and marked necrosis and fibrosis were

Fig. 3 (case 2).—Mycelial form (?) of fungus in nodule from the lung. × 300.

present. In the second case there was very little necrosis and fibrosis, even in the liver, the cells in the involved areas being quite intact although collected in large sheets. The liver showed marked changes in the first case, while in the second it appeared to be essentially normal in many areas except for the filled endothelial elements. The general impression to be gained from a study of the sections was that in case 2 the disease was far less advanced and that only a few areas, such as the abdominal nodes, showed changes approaching those observed in case 1. It is possible that in these areas the disease had been present for a much longer period.

The slide showing the mycelial elements was submitted to Dr. Morris Moore,[11] of St. Louis, who has made a thorough study of the myocologic aspect of this disease. Because of the inadequacy of the preparation, he is hesitant to term the growth a mycelial phase of the yeastlike form found in the tissues but he has stated that he can see many points in common between the two organisms. The

11. Moore, M.: Personal communication to the author.

fact that transition from one form to the other is seen in cultures and animal inoculation adds some weight to the possibility, if the transition is considered to be the result of a particular environment, at a particular point, which is favorable to change. Moore considers the intracellular bodies observed in the 2 cases here reported to be similar to the original Histoplasm capsulatum.

ETIOLOGIC CONSIDERATIONS

The causative organism is unquestionably a fungus. The studies of De Monbreun [4] have since had the support of other mycologists who in 1934 were somewhat divided as to its exact taxonomic status, although the first impressions were that it belonged to the genus Endomyces. In cultures isolated from the spleen and blood in 1 case De Monbreun was able to cultivate the yeastlike form in which the organism was isolated and to convert it to the mycelial form at will, and then, by animal inoculation, to return it to the yeastlike phase. Monkeys inoculated with the cultures presented typical clinical symptoms, and at autopsy the pathologic appearance of the lesions was similar.

At one time Cryptococcus farciminosus, the causative agent of epizootic lymphangitis in horses, was suspected of being the guilty organism, but further studies absolved it. This organism closely resembles the so-called Histoplasma capsulatum; but cultural studies made differentiation possible, and the clinical symptoms of its presence in man are mild and local. Under moderate magnifications the tissue sections in cases of cytomycosis are also distinctly reminiscent of those of kala-azar, but there are no blepharoplasts and the distribution in the tissue is decidedly different.

Moore [11] has recently found the organisms in the prostate in the case of a patient from St. Louis and has had the opportunity of studying some referred cases (including 1 from Iowa City which has been reported by Hansmann and Schenken [12]). He feels that two closely related fungi are responsible for the disease, namely, Histoplasma (cryptococcus) capsulatum, as originally described by Darling, and also a piriform type. These two are quite easily distinguished by their clubbed terminations in the mycelial phase but apparently are indistinguishable in the yeastlike form. In my opinion, there is a very slight difference in the size of the organisms in the 2 cases reported here; this, however, can probably be attributed to the variant mediums in which they grew.

In case 2, sections of the small reddish brown nodule observed near the apex in one lung showed a luxuriant growth of a fungus in the myceliate state. If this mycelial formation is a second phase of the

12. Hansmann, G. H., and Schenken, J. R.: A Unique Infection in Man Caused by a New Yeast-Like Organism, a Pathogenic Member of the Genus Sepedonium, Am. J. Path. **10**:731, 1934.

fungus present in the yeastlike phase in the same person, it is apparently the first time such a phenomenon has been observed. The mycelial growth bears some resemblance to De Monbreun's illustrations of his various cultures, but it lacks the ascus-like bodies he described.

The exact site of entry is uncertain; the skin has been suggested, with possible bites or infestations by parasites, as the mode of entry, but the portal most commonly accepted appears to be the lungs. They at least are the site of the oldest and most dense involvement in many cases, and in 1 case the organisms were observed only in the lungs; while pulmonary foci were absent in 2 cases, it is possible that in these the foci were too minute to be observed. In case 2 it is not difficult to imagine that the reason the myceliate form developed in one nodule in the lung might be that it had been the original focus and was therefore the only one to show this phase.

I think attention can be profitably drawn to the ear as a possible primary focus. In 1 of the cases previously reported otitis media was present during the disease and the organisms were found in the discharge;[7] in another, there was otitis media,[10] and in one of the present cases (case 1) the patient had been treated for a fungous disease of the ear shortly before the onset of the illness. The frequency with which various fungous infections invade the auditory canal also lends some weight to this suggestion.

PATHOLOGIC CHANGES

Descriptions of the gross and microscopic pathologic changes observed in this disease are somewhat discordant, and one recalls the predicament of the 3 blind men of Hindustan. Thus, in 1 case[6] the lungs alone showed the organism in the endothelial cells, and since in this case the patient died from a far advanced visceral malignant process, we are forced to believe that a more general dissemination was prevented and that the disease in question was observed in a rather early stage; in other cases[13] the engulfed blastospores were found only in the adrenal glands. Some of the data from the cases reported in the literature are presented in the table.

Grossly, the spleen appears to be almost invariably enlarged; in 1 case[7] it weighed but 210 Gm. and the authors emphasized that this was a variant to the usual pathologic picture. (However, I feel that a spleen of this size should be considered definitely enlarged.) Of the gross pathologic changes, next in frequency of incidence to splenomegaly are the small nodules (pinhead to pea size) which are observed in the lungs, liver and spleen, in that order of frequency. In more advanced

13. Currie, R. W., cited by Parsons.[10]

Tabulation of Reported Cases

Author Date	Sex Age	Locale	Duration of Illness	Temperature, F.	Spleen	Emaciation	Leukocyte Count	Red Cell Count, Millions	Hemoglobin, %	Other Findings
Darling..... 1905	M 27	Canal Zone	3½ mo.	101	Palpable, large; 3 × normal at necropsy	Moderate	2,200	....	60	Colitis; vomiting (3 mo.)
Darling..... 1906	M 29	Canal Zone	? In hospital for 2 wk.	101	Palpable; 5 × normal	.....	.....	....	..	Headache, emesis, diarrhea
Darling..... 1906	M 55	Canal Zone (China 15 yr. before)	5 mo.	102	Enlarged and firm	Slight	Normal	....	70	
Watson and Riley..... 1926	F 52	Minnesota	8 yr.	102	Large for 8 yr.; 10 × normal: (liver large)	Weight loss of 35 lb. over years	3,000-4,600 67% polys.	3.8	85	Albuminuria; illness marked only last month
Phelps and Mallory.... 1926	M 24	Honduras	7 wk.	101	Large (liver also large)	Marked	7,860	....	60	Carcinoma of liver; vomiting
Crumrine and Kessel... 1931	M 42	Louisiana and California	9 mo.	101-102.5	Nonpalpable; necropsy, 210 Gm.	Weight loss of 33 lb. in 6 mo.	3,000 80% polys.	3.12	70	Colitis 3 mo.; epigastric pain; weakness, cough
Dodd and Tompkins... 1934	M 6 mo.	Tennessee	3 wk.	100	Palpable (liver also)	.....	11,640, 22% P. 63% L.	2.07	40	Pus in middle ear; icterus index 30; early erythrocytes
Amolsch..... 1939	F 8 mo.	Michigan	4 mo.	101-103	Palpable; necropsy, 159 Gm.	Marked	1,500, average 44-55% polys.	2.00	35 to 50	Weakness, cough, otitis media; normoblasts
Humphrey..... 1939	M 18	Michigan	19 mo.	103 remissive	Vague in life; necropsy, 700 Gm.	Moderate	1,200-3,500	1.72-5.2	42-106	Cough last month; epistaxis; normoblasts
Humphrey..... 1939	M 46	Michigan	9 mo.	102.5	Palpable; necropsy, 600 Gm.	Marked	6,200	3.38	58	Weakness, sweats, nausea, vomiting; normoblasts

stages of the disease, however, the nodules are widely disseminated and appear in the intestine, on the peritoneal and pleural surfaces and even in the heart, as in 1 of my cases. They may be uniform or may vary in size; they may be white or pearly gray, and on cross section they may appear seminecrotic, firm or hyalinized. It is probable that these nodules exist in every tissue of the body in far advanced stages, and not, as once stated, only in the viscera rich in free histiocytes and reticuloendothelial elements. Most of these nodules appear hyalinized on section and undoubtedly represent a late phase of the histiocytic aggregations. Intestinal ulceration, sometimes resembling the amebic type, has occurred in several cases. An almost constant gross finding is peribronchial and abdominal perivertebral lymphadenopathy; many of the affected glands attain the size of hens' eggs and appear necrotic on cross section. In several cases the nodes about the jejunum and pancreas formed huge masses, which in 1 instance were palpable through the abdominal wall.

In the first case reported in this paper I felt that at autopsy I was dealing with a generalized sarcomatosis, and I marveled at the duration of life in the face of such a widespread involvement. In the second case the gross pathologic changes were disappointing, as actually the only thing of note was the large spleen and a few small hyaline plaques on the apical pleura of one lung, associated with adhesions of the type commonly observed in this area and with the calcified hilar nodes of healed tuberculosis on the same side.

It is apparent that the gross pathologic changes vary only as the duration or degree of dissemination of the disease may dictate and, as the microscopic study will demonstrate, probably have nothing to do with the resistance of the patient or with similar factors. In many respects the picture resembles the differences observed in the gross findings in patients with a malignant growth; thus, there may be a general miliary carcinomatosis, or, by contrast, only a few nodules in one or two organs.

Microscopically, the parasites occur in various phagocytic cells, such as the endothelial wandering cells of the tissues and the large mononuclear cells of the blood and marrow, as well as in the fixed reticuloendothelial cells of the liver and spleen (for example, the Kupffer cells of the liver). All observers appear to agree that the location of these yeastlike organisms is limited to the reticuloendothelial system and other phagocytic cells [14] and that no other tissue is involved nor are adjacent cells damaged by any toxin from the organisms.

The yeastlike form measures 3 to 5 microns [4] in diameter and consists of an oval or round dark-staining body surrounded by a clear,

14. Watson, C. J.: The Pathology of Histoplasmosis (Darling) with Special Reference to the Origin of the Phagocytes, Folia haemat. **37**:70 (Oct.) 1928.

halo-like capsule. While other stains have been recommended, the organism can in most instances be observed and recognized with some degree of certainty with the high, dry objective of the microscope in sections stained with hematoxylin and eosin. The bodies pack the phagocytic cells in numbers from 1 to 50; they show some variation in staining characteristics, due, no doubt, to degenerative changes.

There appear to be three rather well defined types or stages of lesions. First, there are areas in which isolated phagocytic cells are filled with parasites, or in which collections of these cells form small masses or sheets, such as are observed frequently in the liver. Such isolated cells were present in the glomerular tuft of the kidney in the cases reported here. Neither in the glomerulus nor in the liver does there appear to be a vestige of leukocytic reaction about these cells; and in most instances the untouched cells of the infested organ are unchanged. This is doubtless the earliest phase of the invasion in a particular area. The blood stream has carried one laden histiocyte to lodge in that site, and in a fruitless endeavor to share the burden, other uninvolved phagocytic cells have collected at this point. These in turn become involved by direct extension, and thus a large sheet of these cells develop. This is the probable explanation of the masses in the cardiac muscle, which are somewhat difficult to understand on any other basis.

The second phase results in a somewhat different type of lesion. The long-continued and progressive obstruction of the vessel conveying the original involved phagocyte to the area finally results in necrosis; this change is most marked in the center of the mass, and the phagocytes which have wandered peripherally in the surrounding tissue form a more or less intact ring about the caseating center. In the sections of liver it is interesting to note the regular distribution of these areas. In this phase the continued ischemia appears to affect some parenchymal cells; thus, in the liver the hepatic cells undergo changes and often show areas of fatty degeneration about the histiocytic mass.

The third phase is the end result of necrosis. Fibrous tissue and hyaline masses replace the lesion, and scarcely any laden phagocytes remain; the parasites which remain stain hypochromatically and probably are degenerating. A few plasma cells and lymphocytes are scattered about, and mitotic figures are often observed. In several instances multinucleated cells, which often resembled Reed, or Sternberg, cells, were observed, and even giant cells. In the sections studied by me the cytoplasm of these cells was rather light, and the three or four nuclei were partially superimposed and semivascular.

Obviously, these parasite-laden cells can migrate to any part of the body, and their absence in sections from certain organs must indicate

merely either failure due to random sampling or an early stage of the disease. It is also easily seen that the processes of early isolated histiocytosis, of caseation and of fibrosis or hyalinization can exit contemporaneously in the same patient, although one of the three phases may dominate the picture.

In certain areas fibrosis and hyalinization may reach such proportions that no organisms can be observed. The question is thus raised as to whether a complete cure might not be accomplished in the early stages of the disease.

SYMPTOMATOLOGY

The disease is apparently relentlessly progressive during its course, which may occupy only a few months or weeks, as in the cases of the 2 infants cited in the table, or eight years, as in another instance;[5] there may be long remissions, or the disease may enter the acute phase and terminate rapidly.

Fever (temperature 100 to 105 F.) was the most constant clinical finding, although in three of the reported cases the temperature returned to normal for extended periods. The fever was accompanied by pronounced loss in weight and extreme weakness.

Gastrointestinal upsets, such as diarrhea, nausea and vomiting, occurred in half of the cases; the diarrhea was often extremely severe. It is interesting that there was usually no definite pain.

Despite the pulmonary involvement the only related symptom was cough, present in 3 cases. Epistaxis occurred but once, and there was no hemoptysis. Death occurred usually as the obvious result of increasing inanition, although in 2 cases the finale was extremely rapid.

The spleen was palpable at some time during the course of the disease in most of the cases; occasionally enlargement of the liver was also noted. If one disregards the omnipresent emaciation, the only other significant physical finding encountered was a cervical or abdominal lymphadenopathy, and this in but a few cases. In 2 instances large nodes were palpable through the upper portion of the abdominal wall.

Laboratory findings were only rarely pathognomonic. In 1 instance the organism was noted in the blood smears and cultures; in another, the spleen was removed and the diagnosis was made from the sections of this organ. It is quite obvious, however, that in many instances splenic puncture would have been a valuable diagnostic procedure. Hyperbilirubinemia occurred in 2 cases and albuminuria in 3 others.

In the 7 cases in which the red cell counts were recorded a profound anemia of the aplastic type, probably a result of displacement of marrow, was noted. The number of erythrocytes varied from 3,800,000 to 1,700,000, with an average of 2,600,000; the hemoglobin content was from 35 to 85 per cent. Of 8 cases, the white count was low at some

time during the disease in 5 (below 1,500 in 2), slightly elevated in 1 (11,640) and normal in 2. The differential counts showed normoblasts or megaloblasts in 4 cases; in some of these the anemia was not marked, and one is led to believe that it might be due to an irritative lesion of the marrow.

The ratio of lymphocytes to polymorphonuclear leukocytes varied during the course of the disease in certain cases and also among the various cases. Thus, in 1 case in which there was marked leukopenia the ratio was essentially normal, while in another a constantly recurring agranulocytosis appeared. It is apparent that the character of the blood count depends on the degree of involvement of the hemopoietic tissue by the organism.

DIAGNOSIS

The diagnosis can be made definite only by the detection of the fungus in the phagocytic cells of the blood, in smears from sternal or splenic punctures or in sections of tissue removed at splenectomy. It should be considered in cases in which there are continued fever, splenomegaly and leukopenia.

A severe anemia often occurs in the later stages; it may be hyperchromic and the presence of erythroblastic forms may be noted.

Leukopenic diseases, such as malaria, typhoid, kala-azar, malignant processes involving hemopoietic centers and certain phases of infectious mononucleosis and undulant fever, must be ruled out in the differential diagnosis.

PROGNOSIS, COURSE AND TREATMENT

The course, as has been stated, may be acute, terminating in a few weeks, or the process may extend, with irregular exacerbations or in a chronic form, over a period of years. The general impression is that the disease is invariably fatal, although in some of the recent cases it appears to be concomitant with some entirely unrelated disease which is the direct cause of death. It seems probable that in certain instances the lesions may remain in an arrested state for some time or, possibly, may undergo fibrosis, with a permanent cure as a result.

Treatment has been of no avail. Iodides, ionized metals, roentgen radiation, bone marrow, pentnucleotide and repeated transfusions have been only of transient value. There is no record of the use of sulfanilamide or its variants.

COMMENT

Two cases have been presented in which there were, fortunately, a detailed clinical history and a reasonably good follow-up and necropsy. The organisms were not cultured, however, nor were they observed during life. Luckily, in the 2 cases the disease was disseminated in two distinct phases, so that insight into the pathologic processes attendant

on its course was afforded. I have been able to establish a few facts relative to the pathology and diagnosis of reticuloendothelial cytomycosis by correlating the 7 previously reported cases with the present 2 and with 1 unpublished one.[9] Prior to this time, the paucity and incompleteness of the material have prevented any but a very dubious clinical and pathologic concept. It is hoped that to the list of disorders characterized by pyrexia, splenomegaly and leukopenia another will now be added.

Six other cases have been noted within the last few months in the Mississippi River basin, in addition to the 3 recent ones mentioned; but to my knowledge these have not as yet been reported.[15] The fact that 9 have occurred in the space of a year when only 7 had been catalogued in the preceding twenty-four years is both interesting and alarming. While the yeastlike form of the organism is not prominent in sections of tissue, neither is it so retiring as not to excite comment; I can scarcely believe that the present increase in the number of cases is due to improved diagnostic acumen alone. I do understand that in 2 cases the organisms were not noticed or identified for many months after the sections had been examined; but in the illustrations of the various cases and in my sections they are definite and cleancut oddities.

At first the disease was believed to be tropical, but although Müller a few years ago reported 1 case in Java,[16] all of the recent reports have come from the central portion of North America. It is quite probable that in tropical regions the disease may be submerged by the similar syndromes of kala-azar and malaria so common in those regions, but some reason must exist for the rather abrupt appearance of the disease in the Mississippi River basin. One reason that suggests itself is the increased facility with which men now move from one climatic zone to another; thus the fungus or some parasite conveying it, in either the yeastlike or the mycelial form, may be carried for great distances by plane or automobile before the organism or carrier succumbs to the new environment.

Several articles on the experimental production of this infection in animals have appeared in the Italian literature; recently Redaelli [17] has studied the rate of disappearance of congo red in the circulation in the disease. He describes a relationship between the concentration

15. De Monbreun, W. A.: The Dog as a Natural Host for Histoplasma Capsulatum, Am. J. Trop. Med. **19**:565 (Nov.) 1939.

16. Müller, H.: Histoplasmosis in East Java, Geneesk. tijdschr. v. Nederl.-Indië **72**:889, 1931.

17. Redaelli, P.: Osservazioni e considerazioni su alcuni aspetti anatomici e funzionale del sistema reticolo-istiocitario nella malattia sperimentale da histoplasma capsulatum Darling, Riv. di pat. sper. **16**:1 (Jan.-Feb.) 1938.

of dye and the efficacy of the involved or hypertrophied reticuloendothelial system which may in the future be applied to the study of the disease in man.

SUMMARY

Two cases of histoplasmosis of Darling are presented; the more apt name of reticuloendothelial cytomycosis is suggested, in accordance with the work of De Monbreun. Sufficient cases have now been collected to justify an effort to correlate the varied clinical and pathologic findings in a definite concept which will facilitate clinical diagnosis.

A clinical entity which prior to a year ago was considered a great rarity may become a common and serious problem and should be suspected in all cases demonstrating the not uncommon syndrome of pyrexia, splenomegaly and leukopenia.

It is suggested that increased facilities for transportation may be the cause of the recent increase in the number of cases.

Dr. John D. Littig, of Kalamazoo, Mich., and Miss Lorena Hilbert, of the Pennock Hospital Laboratory, Hastings, Mich., placed excellent records at my disposal.

ACUTE MILIARY INFARCTION OF THE HEART

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AND
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This communication is a report of 99 cases of what we have called acute miliary infarction of the myocardium; the lesion was usually associated with the clinical syndrome of sudden left ventricular failure The material reviewed consisted of 2,857 consecutive cases in which autopsies were performed at City Hospital during the twelve year period between 1927 and 1938, inclusive. These cases were first separated into two groups on the basis of the presence or absence, macroscopically, of moderate or marked sclerosis of the larger coronary

TABLE 1.—*Classification of 2,857 Cases in Which Autopsy Was Performed*

Group	Total Number	Number in Which Acute Miliary Infarctions Were Present	Number in Which Acute Coronary Thrombosis Was Present
1. Cases in which coronary arteriosclerosis was present	983		
(*a*) Cardiac	336	51	42*
(*b*) Noncardiac	647	15	10*
2. Cases in which coronary arteriosclerosis was not present	1,874	9	0

* Of the 52 hearts with acute coronary thrombosis, 24 were studied histologically; all these showed acute miliary infarctions.

arteries. The group in which coronary sclerosis was present was subdivided into (*a*) those in which the primary clinical feature was cardiac dysfunction (cardiac-sclerotic group) and (*b*) those in which the presenting clinical syndrome was noncardiac (noncardiac-sclerotic group). Cases in which acute coronary thrombosis occurred were also grouped separately. The classification is summarized in table 1.

The most prominent characteristics of the acute miliary infarction were sharp definition, the tendency to concentrate on the left side of the heart and the predilection for the deep layers of the myocardium. As to size, the involved area about filled a low power field of the microscope; the shape of it was somewhat irregular (fig. 1). At all stages the lesion was surrounded by well preserved myocardium. All phases of

From the Pathological Laboratory, City Hospital, Welfare Island, Department of Hospitals.

necrosis of the muscle could be seen in various foci. In the early phase the fibers became granular. The granular appearance rapidly gave place to amorphous masses of cytoplasm. As the amorphous masses disappeared, the lipochrome became more prominent. Then the nuclei and the cytoplasm completely disappeared, leaving only the preexisting reticulum and traces of lipochrome (fig. 2). The invading cells were

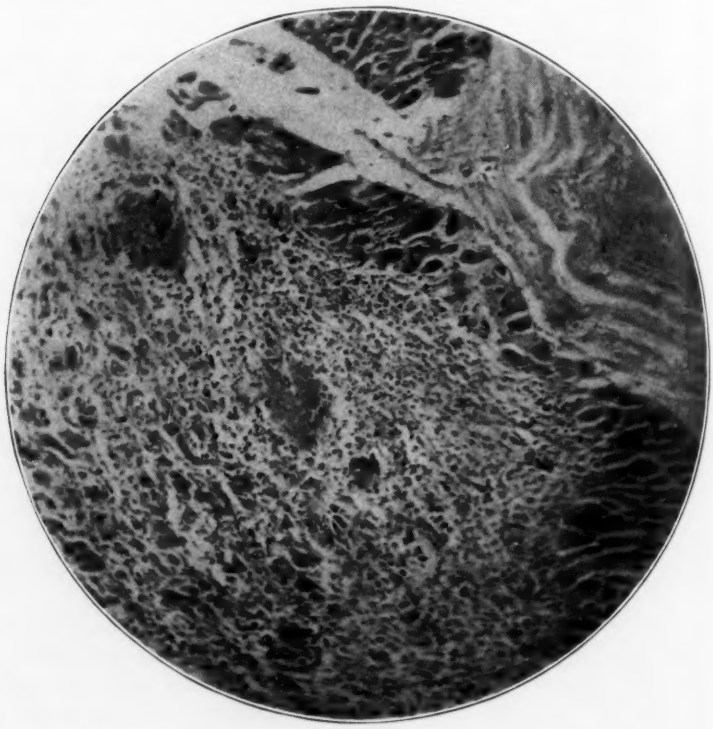

Fig. 1.—The lesion in the acute phase, showing the somewhat irregular shape, the sharp borders and the acute degeneration of the cytoplasm (low power).

largely monocytes, which made their appearance when the cytoplasm, although disintegrating, was still fairly abundant (fig. 3). Polymorphonuclear cells and, more infrequently, some lymphocytes were occasionally found, but they did not constitute a prominent feature. As the cytoplasm was lost, and only the reticulum remained, the invading cells also were affected and likewise disappeared (fig. 4). Fatty degeneration of the fibers in the lesion was conspicuous by its absence. Occasionally

a few fibers of the adjacent myocardium were affected, but in only 2 instances, both in the cardiac-sclerotic group, was there a generalized fatty myocardial change. In both of these cases syphilis was a complication. This myocardial lesion has been described previously in a case reported by Roesler and Soloff.[1]

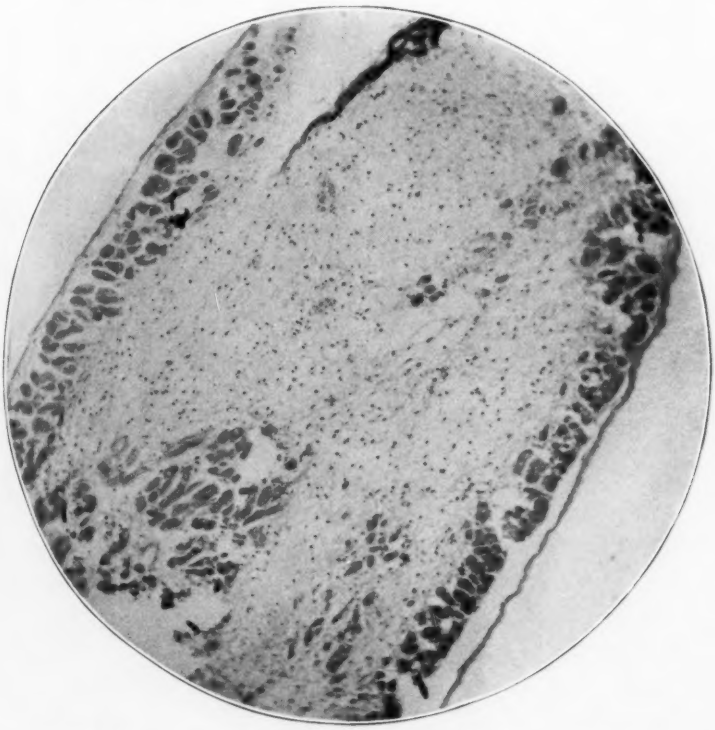

Fig. 2.—The fully developed lesion, showing only the remains of reticulum. This view also shows the location in the deep myocardium and the narrow preserved muscle beneath the endocardium (low power).

The myocardial branches of the coronary arteries were, as a whole, fairly normal. In the larger branches, however, sclerotic changes were not uncommon. Less frequent was medial hypertrophy, usually focal in distribution and never generalized. In 17 cases the small muscular

1. Roesler, H., and Soloff, L. A.: Report of a Case of Left Ventricular Failure with Unusual Anatomical Changes in the Myocardium, Ann. Int. Med. 9:477, 1935.

branches showed acute thrombi or emboli (figs. 5 and 6); 8 of these cases were in the cardiac-sclerotic group (in 1 the source was bacterial); 2 were in the noncardiac sclerotic group; 4 were in the group in which acute coronary thrombosis was noted, and 3 were in the nonsclerotic group (in 1 the source was a primary bronchogenic carcinoma). These thrombi were present only in the walls affected by the miliary infarctions.

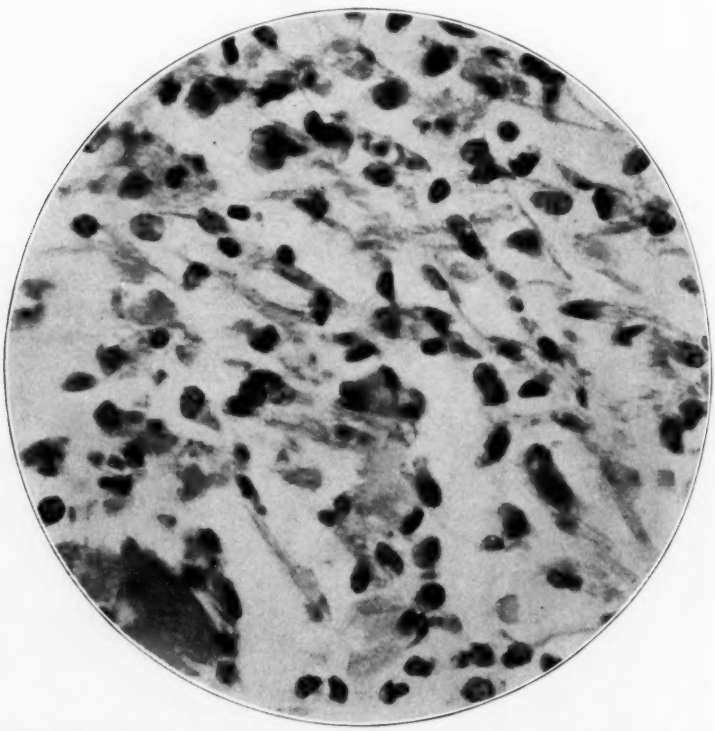

Fig. 3.—High power magnification of the section shown in figure 1. Note the swollen nuclei of the muscle and the remains of cytoplasm, lipochrome and reticulum.

Grossly, the chief characteristics of the hearts in which the lesions were found were soft consistency, pale color and mottled appearance of the myocardium. On transection of the ventricular walls, the pale brown myocardium had a speckled or mottled appearance from the presence of minute foci or streaks, light yellow, fawn colored, gray or gray-yellow. In some hearts the lesions were larger, about the size of a nickel or a quarter, and had all the features of massive cardiac infarction.

It was of interest to note the incidence of these larger lesions in the various groups. Of the 51 cases in the cardiac-sclerotic group, 7 showed the coarse acute infarctions. A fairly large lesion was found in 1 of the 15 cases in the noncardiac-sclerotic group, and among the 9 cases in the nonsclerotic group there were 2 in which macroscopic lesions were noted, one lesion comparatively small and the other massive.

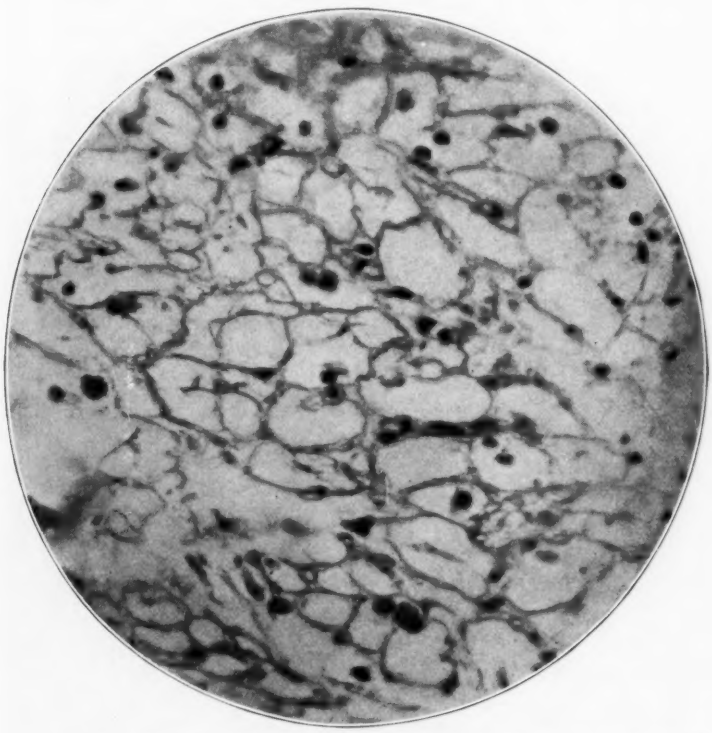

Fig. 4.—High power magnification of the area shown in figure 2. Note the remains of the reticulum. There are still a few remnants of cytoplasm.

Thorough histologic examinations were carried out on the 24 hearts with recent coronary occlusion. Massive recent infarction was absent in 5. Grossly, the myocardium in these hearts showed the characteristics described previously (soft consistency, pale color and mottling), and microscopically there were extensive miliary infarcts. In the remaining 19 hearts, the myocardium beyond the area of massive infarction had similar gross and microscopic features.

Hypertrophy of the heart was frequent (table 2). As can be seen in this table, the weight of the heart in almost 75 per cent of the cases in the cardiac-sclerotic group was 600 Gm. or more, and in only 1 case was the heart not hypertrophied. In most of these cases the cardiac abnormality was associated with hypertension, the systolic blood pres-

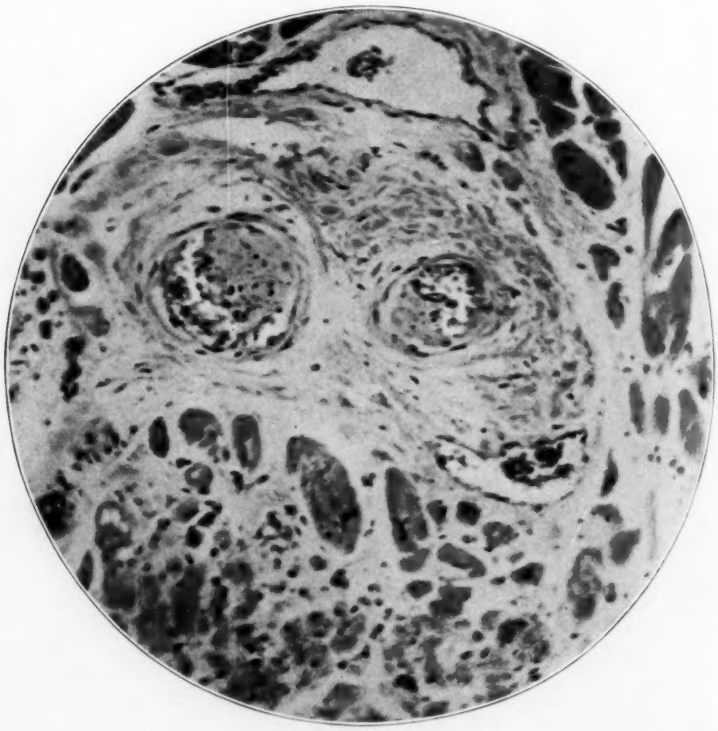

Fig. 5.—Acute thrombosis in a myocardial branch of a coronary artery. Most of the small arteries were normal, as is shown.

TABLE 2.—*Weights of Hearts in Various Groups*

Group	Hearts with Given Weight, Gm.						
	299 and Under	300-399	400-499	500-599	600-699	700-799	800 or More
Cardiac-sclerotic	0	1	6	6	21	11	6
Noncardiac-sclerotic*	0	3	3	3	2	0	0
Acute coronary thrombosis†	0	9	10	13	6	9	2
Nonsclerotic‡	4	0	0	0	1	3	0

* No weight was recorded in 4 cases; in 1 case the heart was noted as enlarged.
† No weight was recorded in 3 cases; all the hearts were enlarged; 1 was very large.
‡ No weight was recorded in 1 case; the heart was noted as small.

sure varying from 155 to over 200 mm. of mercury. Vascular changes of the type associated with essential hypertension were found in the kidneys in all but 5 instances. In the case in which the heart was small, the kidneys and the blood pressure were normal. In 1 case the enlarged heart was due to syphilitic aortic valvulitis with incompetency. In 3 cases there was no evident explanation for the hypertrophy. In

Fig. 6.—Acute thrombosis in some of the hyperplastic small vessels. The view also shows one small vessel free from thrombus.

the noncardiac-sclerotic group increase in the weight of the heart tended to be less marked; when noted, it was usually associated with essential hypertension, as in the other group. In the group of cases of acute coronary thrombosis the greatest extremes in weight were noted, but in general the hypertrophy was of the same hypertensive character. The nonsclerotic group was more heterogeneous. Half the hearts were small, half were very large. The basis of the hypertrophy was essential hypertension in 2 cases (complicated in 1 by chronic active rheumatic

valvulitis), syphilitic valvulitis with incompetence in 1 case, and stenosis of the aortic and mitral valves from healed rheumatic heart disease in 1 case.

The distribution by race conformed to the generally accepted views of the incidence of coronary disease. In the cardiac-sclerotic group there were 39 white persons and 11 colored, in the noncardiac-sclerotic group 14 white persons and 1 colored, in the group with acute coronary thrombosis 43 white persons and 8 colored, and in the nonsclerotic group 7 white persons and 2 colored. There was 1 male Japanese in the first group, and there was 1 male Amerind in the third. The proportion of white to colored patients with acute coronary thrombosis was somewhat higher than that usually recorded, 5.4:1; in the cardiac-sclerotic group the proportion was 3.5:1. In the noncardiac-sclerotic group only 1 of the 15 patients was colored.

The distribution by sex also conformed to the usual views. Of the white persons in the cardiac-sclerotic group 28 were men and 11 were women, of the colored persons, 7 were men and 4 women. In the group with acute coronary thrombosis, of the white patients, 33 were men and 10 were women; of the colored patients, 7 were men and 1 was a woman. In the noncardiac-sclerotic group were 8 white men and 6 white women; the single colored patient was a Negress. In the nonsclerotic group the white women outnumbered the men 4:3; the 2 colored patients were a 10 year old girl and a man.

In most cases the patients were in the later periods of life, from the fourth decade on. The youngest patient, a child of 10 in the nonsclerotic group, and the oldest, a man of 75 with acute coronary thrombosis, were both Negroes. Certain relationships between age, race and sex were noted. Among the patients in the sclerotic-cardiac group, the youngest white man was 41; the youngest white woman was a decade older, 50. The oldest white man and the oldest woman were in the same decade of life, the eighth. Among the colored patients in this group the youngest man was 38 and the youngest woman, 39; both were thus younger than the youngest white patients. The ages of the oldest man and the oldest woman were about the same for the colored as for the white patients, 79 and 68. The findings were similar in the group with acute coronary thrombosis. Among the white patients, the youngest man was 43, the youngest woman, 55; the oldest man and the oldest woman were 92 and 80, respectively, a decade or two older than the oldest of the first group. Similar extremes of age (52 and 95) were found among the colored men. There was only 1 Negro woman, 53. Among the white patients in the noncardiac-sclerotic group there was a reversal of the youngest ages for men and for women: The youngest woman was 40 and the youngest man, 54. The oldest man and the

oldest woman were both 75. The significance of the reversal of the lower limit of age in reference to sex in this group is doubtful. A much larger series might show the usual finding—the women a decade older than the men. The only colored patient in the group was a Negress of 42. The patients in the nonsclerotic group, with the exception of the child mentioned before, were all in the sixth and seventh decades.

The clinical syndrome presented during the terminal phase in the great majority of the cases of all the groups was that of sudden left ventricular failure. The characteristic symptoms, either singly or in various combinations, were sudden extreme dyspnea, profuse perspiration, extreme weakness, marked tachycardia, a pulse of poor quality and apprehension. Cyanosis was common; sometimes it was extreme, and occasionally it was absent. It was of interest to note that when cyanosis was absent and death was not delayed more than a few hours the acute miliary lesions were strictly limited to the left side of the heart. Anginal pain was rarely present during the final attack.

Death was seldom delayed for more than four days. Usually it occurred within twenty-four or forty-eight hours of the cardiac collapse. Sudden death was common: Among patients in the cardiac-sclerotic group it occurred 11 times; among those in the noncardiac-sclerotic group, 4 times; among those with acute coronary thrombosis, 15 times; among those in the nonsclerotic group, 3 times. In the last group the hearts of 2 patients were greatly hypertrophied. Although anginal attacks had occurred previous to death in very many of the cases, sudden death occurred in 5 patients in the cardiac-sclerotic group and in 1 patient in the group with acute coronary thrombosis who had no attack of angina and in whom cardiac failure had been of a congestive nature. Four patients of the noncardiac-sclerotic group and 3 in the group with acute thrombosis had no history of previous cardiac disability.

From the histories, the attacks of cardiac dysfunction that occurred prior to death were usually of the type recognized as characteristic of coronary sclerosis. Anginal pain or its equivalent had been experienced for varying lengths of time previous to the final episode. In the cardiac-sclerotic group such pain occurred in 36 of 49 cases; in the group in which acute coronary thrombosis was present, in 27 of 42; in the nonsclerotic group, in 3 of 8. It occurred in only 1 case in the noncardiac-sclerotic group; in this instance a single attack of pain was experienced four months prior to death. In the 3 cases in the nonsclerotic group the heart was hypertrophied. In the remaining cases the data were insufficient to establish the previous history, usually because the patient's statements were unreliable or because death occurred soon after admission to the hospital.

Although it is not of primary interest in this paper, it seems worth noting that many hearts showed evidence of good healing in lesions that seemingly were of the character of miliary infarctions. These healing lesions may possibly explain the previous acute episodes from which the patients had recovered.

Of the possible etiologic factors, there is, first, arteriosclerosis of the coronary arteries. Throughout the entire series of cases there was no uniformity in the condition of the superficial coronary arteries. In the nonsclerotic group, they were normal. Marked degrees of sclerosis were present in about half of the cases (9) in the noncardiac-sclerotic group, in about two thirds of the cases (35) in the cardiac-sclerotic group and in almost all of the cases (50) in the group in which acute thrombosis was noted. Except for the last group, in which the lumens of the coronary arteries tended to be narrowed, it was noted that with marked changes of the coronary walls, the lumens were as frequently wide as narrow. Old thromboses were noted with a frequency about parallel to the degree of arteriosclerosis: in 2 cases in the noncardiac group, in 9 in the cardiac-sclerotic group and in 14 in the group of cases in which recent thrombosis was present. The wide variation, then, of the condition of the coronary arteries militates against arteriosclerosis being in itself the precipitating factor in acute miliary infarctions.

Syphilis of the aorta was found 14 times in the entire series. A history of syphilis was given in 1 case, but its presence could not be demonstrated at autopsy. Involvement of the arch of the aorta or of the commissures, resulting neither in valvular deformity nor in stenosis of the mouths of the coronary arteries, was present in 8 cases. The syphilis in these cases seems an incidental finding, unrelated to the acute myocardial lesion, since in all cases the more severe degrees of arteriosclerosis were present. Isolated atresia of the mouth of one or of both coronary arteries was present in 3 cases. In 1 of these atresia of the mouth of the right coronary artery was associated with acute thrombosis of the anterior descending artery. In a second case atresia of both mouths, with acute thrombosis of the right coronary artery, was complicated by chronic active rheumatic valvulitis and superimposed acute endocarditis. The third case, in which there was atresia of both mouths, was complicated, as were the other 2, by marked arteriosclerosis. The complicating factors rendered it unlikely that syphilis was the sole agent causing the miliary infarctions, although the combination may be of some significance.

An incompetent aortic valve was present in 3 cases. In the first, in the cardiac-sclerotic group, there was atresia of the mouth of the right coronary artery; the miliary infarctions were in the left ventricle and

interventricular wall in the areas supplied by the left coronary artery. In the second case, in which, likewise, the mouth of the right coronary artery was affected, there were acute thromboses of the left circumflex and anterior descending arteries. In the third case, in the nonsclerotic group, a massive acute infarction was present. This, then, remains the single instance in which syphilis seems to have played a definite role. On the whole, however, it seems justifiable to state that syphilis plays a minor role in the entire group.

Lesions of rheumatic heart disease were found in 8 cases—1 in the cardiac-sclerotic group, 3 in the noncardiac-sclerotic group, 2 in the group in which acute thrombosis was present and 2 in the nonsclerotic group. In 1 case each of the first and third groups, the lesions were chronically active. The others were healed. In all cases, stenosis of the mitral valve or of the mitral and aortic valves was present. That rheumatic disease as such has any bearing on the production of miliary infarction seems very doubtful; to the best of our knowledge, the lesion has never been described in reports of cases of active rheumatic carditis, nor have we seen it in such cases in this laboratory. However, rheumatic disease may have some bearing because it may produce a stenotic aortic lesion which in itself is known to render a heart susceptible to any damage.

Roesler and Soloff were of the opinion that in their case a toxic element arising from acute pneumonia was the causative factor underlying the acute myocardial lesion. In this series, also, infection was present in a large majority of the cases. Bacteria were never demonstrated within the lesion itself in any instance. In a case previously reported,[2] thrombosis of a main coronary artery was precipitated by gram-positive cocci, enmeshed in fibrin, originating in acute lobar pneumonia.

Of the 17 cases in which there was acute thrombosis or embolism of the intramuscular branches of the coronary arteries, bacteria were demonstrable in 1 case; they probably arose from a chronic infection of the lower genitourinary tract. Of the remaining 16 cases, an acute infectious process was present in 11. In 1 case in the nonsclerotic group the heart was hypertrophied as a result of chronic active rheumatic valvulitis and essential hypertension, and acute endocarditis of the mitral valve and acute bronchopneumonia were present.

There were 2 instances of infection in the noncardiac-sclerotic group. In 1 case, after cholecystectomy, a nonhemolytic streptococcus was isolated; cellulitis developed at the site of incision and bronchopneumonia ensued. Death was sudden. In the second case an obstruction-infection

2. Lisa, J. R.: Unusual Findings in a Case of Acute Coronary Thrombosis, Arch. Path. **23**:449 (March) 1937; Proc. New York Path. Soc., 1936-1937, p. 3.

syndrome developed after prostatectomy; the patient died suddenly after having had one anginal attack a few days previously.

In 2 of the cases in which acute coronary thrombosis was a feature an acute pneumonic process was noted. In 1 of these there were anginal symptoms, and a genitourinary obstruction-infection syndrome developed as a result of urethral stricture. In the other case lobar pneumonia was present, and the signs and symptoms were primarily pulmonic.

There were 4 instances of bronchopneumonia and 2 of lobar pneumonia in the cardiac-sclerotic group. The cases of lobar pneumonia were of special interest. A Negro woman of 39, who had suffered from congestive heart failure and angina for ten months, had a terminal illness of two days' duration, with severe congestive heart failure and signs of pulmonic consolidation. The pneumonia was in the gray stage at death; it was evidently several days older than the history indicated. In the second case the patient was a white man of 72 who had had sudden severe congestive heart failure for only three weeks before death.

The 82 cases in which thrombi were not found are still to be considered. This number includes 20 of the 24 cases in which acute coronary thrombosis was present in which thorough histologic studies were carried out.

In the nonsclerotic group there were 2 cases in which acute infection was present. The 10 year old Negro girl had generalized miliary tuberculosis; a white woman with Hodgkin's disease had bilateral suppurative maxillary gland infection and bronchopneumonia. Acute infection was present in 9 cases in the noncardiac-sclerotic group. In 4 cases there were acute cerebrovascular accidents and bronchopneumonia. In 1 case there was chronic pulmonary tuberculosis and acute coccal bronchopneumonia. In 1 case there was prostatic hypertrophy with an obstruction-infection syndrome, and the blood culture was positive for Bacillus proteus. In another, general peritonitis developed following rupture of a senile uterus in which septic endometritis was present secondary to stenosis of the external os. In another case, after an amputation for diabetic gangrene, there was a septic course for four days. In the last case there was uremic coma with bronchopneumonia.

In 9 of the cases in which acute coronary thrombosis was noted there were infections. In 1 case there were massive cerebral hemorrhage, acute lobar pneumonia and acute suppurative nephritis; gram-positive cocci were found in sections of the kidney. In 6 cases there was acute bronchopneumonia, once with empyema, once with embolic glomerulitis and once with acute miliary myocardial abscesses. In another case there was a carbuncle of the back, and in the sixth case there was acute endocarditis and the blood culture was positive for Streptococcus haemolyticus. Acute infection was present in 22 instances in the

cardiac-sclerotic group. In most of them the infection was acute bronchopneumonia, although each of the following conditions was found once: cellulitis of the leg, carbuncle, acute pulmonary tuberculosis and infection of the lower genitourinary tract. In 3 cases pneumonia was complicated by empyema; in 1, by pericarditis. It was of interest to note that the temperature seldom was a good indication of infection. In many cases, even when extensive inflammation was present, the temperature was never above 100 F.; the clinical syndrome was cardiac.

Chronic infections were present in 19 of the remaining 40 cases: 1 in the nonsclerotic group; 3 in the noncardiac-sclerotic group; 4 in the group in which coronary thrombosis was recorded, and 11 in the cardiac-sclerotic group. In most of these the infection was chronic tubular bronchiectasis, although pelvic infection and chronic tuberculosis were also found. It should be stated in passing that in many cases acute bronchopneumonia followed chronic bronchitis of the same type. Two factors were noted which might have been the basis for increased susceptibility to the toxic effect of infection in this group of cases. With three exceptions, in all cases there was extreme cardiac hypertrophy, and in most of them, severe arteriosclerosis. In almost half of the cases there were old canalized thrombi in the superficial coronary arteries.

Infection was not demonstrated in the remaining 26 cases; there was a suggestive finding in 1 case only; this was in a case in the nonsclerotic group in which sudden death occurred in the convalescent period after pneumonia. Of the entire series, however, infection was demonstrable in practically 75 per cent of the cases.

If infection, particularly pneumonia, is a causative factor in precipitating acute miliary infarctions, the occurrence of the latter should correspond closely to the winter months. In this series, 65 instances of miliary infarction occurred in the period from November to April, and 34 in that from May to October. In the latter group, active infections were present in 58 per cent of the cases. It is of interest to note also that most of the cases in which chronic purulent bronchiectasis was unassociated with acute bronchopneumonia were included in the winter group.

SUMMARY AND CONCLUSIONS

An acute lesion of the myocardium called miliary infarction is reported. It was found in 99 cases and was usually associated with the clinical syndrome of sudden left ventricular failure. The material reviewed consisted of 2,857 cases in which autopsy was performed; it was divided into two main groups: (1) cases in which coronary arteriosclerosis was present and (2) cases in which this condition was not present. The first group was subdivided into a cardiac-sclerotic group

and a noncardiac-sclerotic group on the basis of clinical symptomatology. The lesion was most frequent in the cardiac-sclerotic group, much less so in the noncardiac-sclerotic group and least frequent in the non-sclerotic group. In the cardiac-sclerotic group its incidence was equal to that of acute coronary thrombosis. The greatly hypertrophied heart with marked sclerosis of the coronary arteries seemed the most susceptible to the occurrence of the lesion.

In 17 of the 99 cases, thrombi or emboli of the myocardial branches of the coronary arteries were found. The thrombosis was bacterial in 1 instance and malignant in another. In 1 case thrombosis of a main coronary artery was caused by a bacterial embolus arising from acute lobar pneumonia. An infectious nature of the myocardial lesion itself was never demonstrated. Infections in other organs, most frequently the lungs, were present in the majority of cases.

It is our opinion that the lesion in the majority of cases is toxic in nature and in a small percentage is due to embolism or thrombosis of the muscular branches of the coronary arteries, usually, even in this group, associated with infection.

SULFANILAMIDE IN TREATMENT OF INFECTIONS OF THE URINARY TRACT DUE TO BACILLUS COLI

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It is common knowledge that once the colon bacillus leaves its normal habitat it sets up inflammation and causes acute or chronic disease in different organs. The two most frequent locations for such disease are the biliary and the urinary tract. In the urinary tract the colon bacillus finds an enviroment that is favorable for its growth. It would appear that the factors which permit the survival and growth of the colon bacillus in the urinary tract are (1) conditions which cause stasis of the urine and (2) the chemical composition and reaction of the urine.

In the treatment of such infections of the urinary tract two methods are in general use: (1) those which relieve conditions that favor stasis of urine and (2) those which change the reaction and chemical composition of the urine so that the organisms have difficulty in surviving.

To relieve stasis, obstructions to the free flow of urine are removed or relieved. To change the reaction and chemical composition of the urine, methods that make the urine more acid or cause the urinary excretion of chemicals which have an unfavorable effect on the growth of the colon bacillus are in common use.

One of the chemotherapeutic agents that have had wide use within the past three years in the treatment of infections of the urinary tract is sulfanilamide. Imhauser and Huber [1] were among the first to call attention to its possible value, and with the appearance of the report by Kenny and his co-workers [2] its use was placed on a rational footing. They studied 46 cases of acute pyelitis and found that the urine was easily sterilized in all cases when moderate doses of the drug were given by

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1. (*a*) Imhauser, K.: Ueber die Behandlung septischer Erkrankungen mit Prontosil, Med. Klin. **31**:282, 1935. (*b*) Huber, H. G.: Ueber Prontosil bei der Behandlung der kindlichen Pyurie, München. med. Wchnschr. **83**:2014, 1936.

2. Kenny, M.; Johnston, F. D.; von Haebler, T., and Miles, A. A.: P-Amino Benzene Sulphonamide in Treatment of Bacterium Coli Infections of the Urinary Tract, with a Note on the Two-Plate Bacterial Count, Lancet **2**:119, 1937.

mouth. The etiologic agent in all of their cases was the colon bacillus. In vitro studies with the organisms from these patients revealed that there were marked variations in the sensitivities of different strains to the drug, and that both bacteriostatic and bactericidal effects were demonstrable in varying degree. No correlation was demonstrable between the ease of producing clinical sterilization of the urine and the resistance of the homologous organism to sulfanilamide in vitro.

Since that time many articles have appeared on the subject, the most noteworthy being those of Helmholz,[3] who described the marked bactericidal effects of the drug in vitro on all the bacteria commonly found as causative agents in infections of the urinary tract, including Escherichia coli, Bacillus proteus, Aerobacter aerogenes, staphylococci and all streptococci except Streptococcus faecalis. Helmholz also postulated that the bactericidal effect noted in vitro was greatly enhanced in an alkaline urine (p_H 6.5 or greater).

The majority of the other reports [4] have discussed the use of sulfanilamide in the treatment of infections of the urinary passages associated with obstructions or other gross abnormalities of these organs, of the type usually seen in urologic or surgical wards. For this reason we began a study of the acute infections of the urinary tract so frequently seen in the medical wards. This paper presents the clinical data for 17 cases of patients with infections of the urinary tract and the bacteriologic studies made in vitro on organisms isolated from the urine of these patients.

The diagnosis of pyelonephritis was made in those cases in which chills, fever and pain in the flanks, with or without dysuria and frequency, were the prominent clinical features. When dysuria and frequency occurred with only minimal evidence of disease in the upper part of the urinary tract, the condition was interpreted as a local cystitis. In both diseases, bacilluria and pyuria were marked and the colon bacillus was initially isolated in pure cultures. Hypertension and albuminuria were absent and the eyegrounds were normal in every case. The excretion of casts was normal; an abnormal number of red blood cells was found in the urine only in those instances in which the symptoms of cystitis were present.

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3. Helmholz, H. F.: Bactericidal Power of Urine After Administration of Prontylin by Mouth, Proc. Staff Meet., Mayo Clin. **12**:244, 1937. Helmholz, H. F., and Osterberg, A. E.: Rate of Excretion and Bactericidal Power of Sulfaniiamide (Prontylin) in Urine, ibid. **12**:377, 1937.

4. Vest, S. A.; Hill, J. H., and Colston, J. A. C.: Experimental and Clinical Observations on Sulfanilamide in Urinary Tract Infections, J. Urol. **41**:31, 1939. Buchtel, H. A., and Cook, E. N.: The Use of Sulfanilamide in Treatment of Urinary Infections, Proc. Staff Meet., Mayo Clin. **12**:444, 1938. King, K. B.: Treatment of Urinary Infections with Particular Reference to Sulfanilamide, Internat. Clin. **3**:208, 1938. Young, H. H., and Vest, S. A.: Treatment of Hematogenous Nephritis with Sulfanilamide, Ann. Surg. **108**:828, 1938.

All specimens of urine from women were collected by sterile catheterization; the infecting organism was isolated on eosin methylene blue and blood agar plates, and the number of organisms was estimated by appropriate serial dilution, 1 cc. of each dilution being poured in plain agar plates. Sulfanilamide in blood and urine was estimated by the method described by Marshall.[5] The excretion of formed elements in the urine was estimated in a selected group by the method described by Addis,[6] in certain instances timed and concentrated, and in others timed but unconcentrated, specimens of the urine being used. The sedimentation rate was measured by the method of Rourke and Ernstene[7] by which the values are expressed in millimeters of settling during the period of most rapid fall.

ANALYSIS OF CASES

The data from 14 of the 17 cases are summarized in table 1. The other 3 cases will be discussed in greater detail because they present many interesting features which require emphasis.

The cases were divided into four groups on the basis of underlying or predisposing processes. It will be demonstrated that the effectiveness of the drug, as judged by its ability to sterilize the urine and assist in eventual cure, varies in each group.

Group 1. Infection of the Urinary Tract Associated with Pregnancy.—The data for cases 1 to 4 in table 1 summarize the pertinent facts in the cases of 4 young women in whom severe to moderately severe acute pyelonephritis developed in the second or third trimester of an otherwise uneventful pregnancy. In the first 3 cases the temperature had returned to normal and most of the symptoms had subsided on a regimen of rest and administration of large volumes of fluid, but bacilluria and pyuria were persisting, when the drug was first administered. Treatment with sulfanilamide was followed by permanent sterilization and clearing of the urine in 2 cases. In the third the medication was irregular and the concentration of sulfanilamide in the blood and urine was low. While marked reduction was noted in the total number of organisms excreted, they never completely disappeared, and the patient was discharged from the hospital free of symptoms but with persistent bacilluria.

Case 4 is of great interest; the clinical course is shown in chart 1. The patient was admitted with symptoms and signs of pyelonephritis

5. Marshall, E. K., and Litchfield, J. T., Jr.: The Determination of Sulfanilamide, Science **88**:85, 1938.

6. Addis, T.: Formed Elements in the Urinary Sediment of Normal Individuals, J. Clin. Investigation **2**:409, 1926.

7. Rourke, M. D., and Ernstene, A. C.: A Method for Correcting the Erythrocyte Sedimentation Rate for Variations in the Cell Volume Percentage of Blood, J. Clin. Investigation **8**:545, 1930.

which were so severe that the diagnosis of a complicating perinephric abscess was entertained. She was acutely ill, and the urine contained many bacilli and leukocytes. After the infection had continued to remain active for a period of one month in spite of the usual methods of treat-

TABLE 1.—*Data on Fourteen*

Case	Age	Sex	Duration of Disease at Beginning of Treatment, Days	Daily Dose of Sulfanilamide, Gm.	Duration of Treatment, Days			Maximum Unacetylated Sulfanilamide, Mg. per 100 Cc.		Urine		
					Total	First Sterile Urine Observed	After Sterilization of Urine	Urine	Blood	pH	No. of B. coli per Cc. Before Treatment	No. of B. coli per Cc. After Treatment
1	33	F	12	3	12	3	8	....	...	5.9	95,000,000	0
2	25	F	20	2	8	3	5	50.0	4.1	6.0	125,000,000	0
3	18	F	15	2	9	..	0	23.0	2.5	6.8	200,000	6,000
4	27	F	38	4	5	4	1	50.0	...	...	120,000,000	0
			4	4	10	3	7	65.0	3.4	...	90,000,000	0
5	19	F	15	3	5	6	0	70.0	7.3	6.4	35,000,000	0
6	28	F	45	2	19	12	7	57.5	4.3	6.5	170,000	0
7	31	F	7	8	6	3	3	....	...	...	1,000,000+	0
8	40	M	18	3	17	0	..	....	...	...	Very many	..
			45	4-6	17	5	12	93.0	3.8	6.5	50,000,000	0
			67	5	20	..	0	139.0	6.7	6.2	1,000*	1,000*
9	26	M	4	5	10	10	0	42.4	9.6	6.4	1,000,000+	0
10	60	F	365+	2	16	..	0	41.0	9.5	5.7	125,000,000	43,000
11	50	F	360+	3	13	..	0	70.0	7.5	7.2	1,000,000	1,000
12	30	F	14	3	5	..	0	44.0	8.5	5.7	30,000,000	1,200
13	35	F	21+	3	5	5	0	100.0	10.0	7.0	125,000,000	0
14	27	M	22	4	8	..	0	63.8	6.1	...	50,000	0
			7	4	9	..	0	....	...	...	Innumerable	0†
15	31	M	11	5.0	13	..	..	92.0	8.7	6.6	19,000,000	160,000
			33	5.0	4	..	..	45.0	...	...	10,000,000	23,000
			102	3	34	1	33	82.9	6.3	...	1,850,000	0
16	53	F	30+	8	7	..	..	68.0	7.2	6.5	106,000,000	1,000
			40	6	5	..	..	32.2	...	...	.....	10,000,000
17	23	F	28	3	9	2	7	101.0	5.0	6.0	1,000,000	0
			43	3	21	3	18	78.4	4.0	7.4	3,000,000	0
			4	8	15	6	9	363.0	13.7	7.0	40,000,000	0

* Staphylococcus albus.
† After mandelate therapy.

ment, sulfanilamide was exhibited by mouth. Within three days the urine was sterile; the patient felt well, and the medication was stopped. Bacteriologic and clinical relapse occurred after five days, but the symptoms were again relieved by the administration of the drug. Four months later she was well. She had no further symptoms referable to

the urinary tract and the renal function was normal. An uneventful labor had taken place in the interval.

From these cases, one can say that 2 to 3 Gm. of sulfanilamide, given in divided doses over a twenty-four hour period, were adequate to effect

of the Seventeen Cases

Clinical Diagnosis	Complicating Factors	Retrograde Pyelograms	Follow-Up	
			Days	Results
Very severe acute pyelonephritis	Pregnancy, 5 mo.; acute bronchitis	None	30	Urine sterile; well
Moderately severe acute pyelonephritis	Pregnancy, 5 mo.	None	360	Urine sterile
Moderately severe acute pyelonephritis	Pregnancy, 8 mo.	None	6	10,000,000 B. coli per cc. urine
Severe acute pyelonephritis	Pregnancy, 7 mo.	Normal	4	Recurrence
Recurrence	.....	.....	140	Well; urine sterile
Mild acute pyelonephritis; cystitis	Acute bronchitis	None	30	Urine sterile
Very severe pyelonephritis; cystitis	Severe acute bronchitis	None	180	Well; urine sterile
Very severe acute pyelonephritis	None	Slight dilatation minor calyces	45	Well; urine sterile
Severe acute pyelonephritis and cystitis	Moderate chronic prostatitis	Normal	10	Cystitis, severe
Severe cystitis; a relapse	.....	.....	5	Cystitis, mild
Mild cystitis; a relapse	.....	.....	None	
Very severe acute pyelonephritis	Hypospadias	Right pelvis dilated, left kidney rotated	7	Well; urine sterile
Cystitis	Hodgkin's disease; chronic pyelonephritis ?	Normal	None	
Cystitis	Diabetes mellitus; chronic cystitis	Normal	350	Well; 100,000 B. coli per cc. urine
Severe acute pyelonephritis	Acute tracheitis; chronic cystitis	Normal	None	
Severe acute pyelonephritis	Chronic pyelonephritis; rheumatic heart disease with decompensation	Slight dilatation right pelvis	180	Many B. coli in urine
Moderately severe acute pyelonephritis	Chronic pyelonephritis	Slight dilatation pelves	14	Recurrence
Acute pyelonephritis; a relapse	.....	.....	90	Well; urine sterile
Severe acute pyelonephritis; B. coli septicemia	None	Double renal pelvis, left	500	Well; 2 attacks of cystitis and 1 of perineal pain with fever since discharge
Very severe acute pyelonephritis	None	Right superior calyx markedly narrowed and irregular	Died	
Acute pyelonephritis	Chronic pyelonephritis	Right pelvis dilated; ureter kinked	3	Bacilluria recurred
Recurrence	.....	.....	4	Bacilluria recurred
Recurrence	.....	.....	365	Bacilluria present; chronically ill

sterilization of the urine in 3 cases of pyelonephritis of pregnancy. In 1, its exhibition was twice associated with a disappearance of the fever and with clinical improvement. In the fourth case the treatment was inadequate, but the total excretion of organisms was reduced without sterilizing the urine. In all of the cases there were no further symptoms

referable to the urinary tract after discharge from the hospital, and the pregnancy terminated normally in each case. This study serves to emphasize the fact that the drug should be continued until all symptoms and signs of pyelonephritis have disappeared. It should be added that the sterilization of the urine occurred without any preliminary alterations in the reaction of the urine and that the best results were obtained when the concentration of sulfanilamide in the urine was 50 to 100 mg. per hundred cubic centimeters.

Group 2. Pyelonephritis with No History of Previous Infection of the Urinary Tract.—In this group there were 6 cases—cases 5 to 8 in table 1 and 2 others which will be considered later. Cases 5 and 6 were those of patients with moderately severe to severe acute infections of the

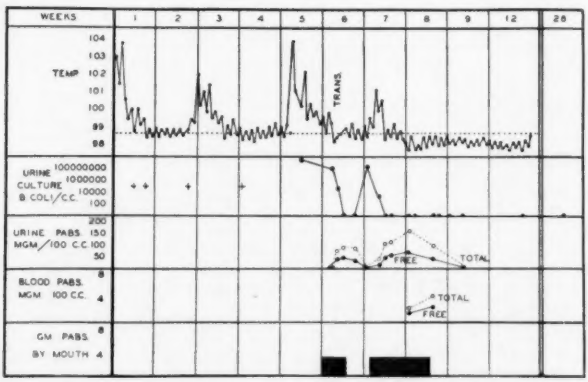

Chart 1.—Course of events in case 4. In this and in succeeding charts, *PABS* indicates sulfanilamide.

kidney whose clinical cure had been obtained by rest in bed and induction of an increase in the output of urine. Sulfanilamide was given to these patients in an attempt to eradicate the bacilluria and pyuria which persisted after the signs of acute infection had disappeared. In both cases the urine was sterilized within three and twelve days, respectively. When the patients were reexamined after one and six months, respectively, they were well and the urine was sterile.

Case 7 was that of a young woman who suffered from a very severe, prostrating infection. Sulfanilamide was administered at the height of the disease; its administration was followed by disappearance of the symptoms and signs of infection and by sterilization of the urine within three days. The patient had a severe reaction, with headache and nausea, so that clinical improvement was delayed until the withdrawal and elimination of the drug. Once the latter was accomplished, she promptly became well, and had continued so when seen one month later.

Case 8, which was similar to case 7, was that of a man in whom dramatic clinical improvement, with clearing of the urine, took place after the administration of sulfanilamide; all symptoms recurred after the withdrawal of the drug and again subsided on its administration. A mild cystitis, associated with the appearance of Staphylococcus albus in the urine, failed to respond to a third course, although a high concentration of the drug was obtained in the urine and blood. A progressive, slowly developing anemia had prompted the termination of the first course but did not recur on subsequent occasions when the drug was given in large doses for a prolonged period.

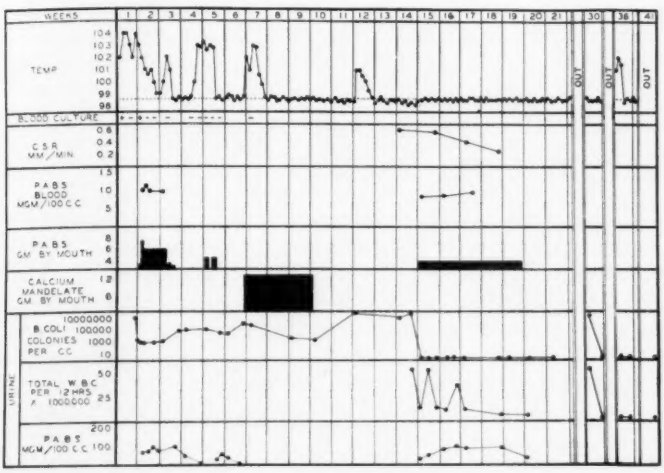
WEEKS
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 30 36 41
TEMP
104 103 102 101 100 99 98
OUT
OUT
OUT
B. COLI CULTURE
C S R MM./MIN.
0.6 0.4 0.2
P A B S BLOOD MGM./100 C.C.
15 10 5
P A B S GM. BY MOUTH
8 6 4
CALCIUM MANDELATE GM. BY MOUTH
12 8
URINE
B. COLI COLONIES PER C.C.
10000000 1000000 1000 10
TOTAL W.B.C. PER 12 HRS. X 1000000
50 25
P A B S MGM./100 C.C.
200 100

Chart 2.—Course of events in case 15.

The following 2 cases, presented in detail, are instructive.

Case 15.—A young man was admitted to the hospital complaining of chills, fever and malaise after the passage of a urethral sound, which had been introduced in the course of an investigation of the sterility of his wife. There was a history of gonorrhea, but he had never had any previous infection referable to the renal system. The physical examination suggested the presence of an acute right-sided pyelonephritis. The urine contained many white blood cells, and the blood and urine cultures were positive for the colon bacillus. Subsequent retrograde pyelograms revealed that the pelvis of the left kidney was double, but the urine from this kidney was normal. The urine from the opposite ureter showed a very great number of leukocytes and bacteria. The course of the patient's illness is illustrated in chart 2.

The administration of sulfanilamide in doses of 5 Gm. per day was begun shortly after the patient's admission to the ward and was followed by clinical improvement; the temperature returned to normal, the blood was sterile on cul-

ture and there was marked reduction of the total number of bacilli in the urine. The development of anemia prompted the discontinuance of this medication. Fever and all other symptoms recurred within five days. The exhibition of the drug was again followed by very marked clinical improvement, although there was practically no effect on the number of excreted bacteria. The use of sulfanilamide was therefore again discontinued. Another acute exacerbation of the disease followed but subsided without medication. The administration of 12 Gm. of ammonium mandelate per day, under controlled conditions which caused the excretion of an acid urine of limited volume, was begun, and it was continued for fifteen days without significant effect on the persisting evidences of infection.

Since the patient failed to return to full health and the urine continued to contain many white blood cells and bacteria, sulfanilamide was again exhibited, in a dose of 3 Gm. per day, for five weeks. With this regimen the urine became sterile within twenty-four hours, the excretion of cells and the erythrocyte sedimentation rate returned to normal and the patient gained weight and felt well.

One month after discharge from the hospital the patient suffered a severe attack of cystitis, with bacilluria, which subsided promptly without medication. Two months later there was a brief period of pain in the perineum and fever of undetermined origin. After that time he remained absolutely well until recently, eighteen months after the acute onset, when the cystitis recurred, accompanied by bleeding after micturition.

It was of considerable interest that sulfanilamide in large doses failed to sterilize the urine in the early stages of the illness, although its administration was apparently accompanied by clinical improvement and sterilization of the blood. Later, after the acute phase had subsided, a smaller dose of the drug was followed by immediate sterilization of the urine, with a concomitant gain in weight and return to good health. Three subsequent events, cystitis on two occasions and an undiagnosed fever with pain in the region of the perineum, suggested that the infection was not eradicated from the genitourinary tract at the completion of the final course of sulfanilamide, but each attack has subsided uneventfully. The course has indicated that no infection remains in the kidney but that the prostate gland is still the site of active disease.

It should be pointed out that anemia developed during the use of the drug in the acute phase of the disease but did not recur when the drug was exhibited later, after the temperature became normal, for a prolonged period.

Case 16.—A woman of 53 was admitted to the hospital with a history of chills, fever and malaise for a short time but without localizing signs or symptoms of infection except for a few rales at the base of the right lung. There was no history of any previous acute illness. Retrograde pyelograms revealed a normal left kidney and some deformity of the superior calix of the right kidney. The patient's course in the hospital is illustrated in chart 3.

Bacilluria was present during the patient's second week in the hospital but sulfanilamide was not used until a colon bacillus bacteremia was discovered during the fourth week. The administration of the drug was followed by a fall in temperature and reduction in the number of organisms in the urine, but the blood

was not sterilized and the development of moderate anemia suggested the withdrawal of the drug. This event, however, was followed by such a severe exacerbation of all symptoms and signs that sulfanilamide was again given, but this time it had no effect on the course of the disease. The patient died in the seventh week of her illness.

Autopsy revealed a normal right kidney. In the left kidney there was a small stone in the inferior minor calyx; the mucosa of the pelvis was greatly inflamed and was sloughing; throughout the cortex there were a number of small abscesses, and there was thrombophlebitis of the small renal veins.

This case again suggests that sulfanilamide may favorably influence the course of acute pyelonephritis without sterilizing the urine, as evidenced by the apparently good effects of the drug when it was first used

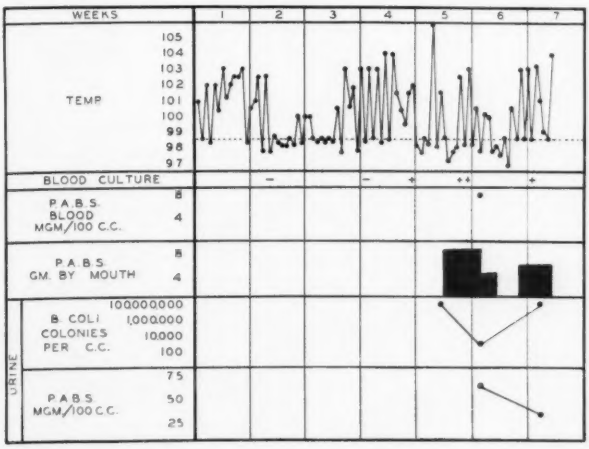

Chart 3.—Course of events in case 16.

That it should have been discontinued is unfortunate, but it is doubtful that the patient could have ever recovered without removal of the kidney, in the light of the existing thrombophlebitis of the intrinsic renal vessels.

The course of the disease in this instance emphasizes the fact that severe acute infections of the kidney are potentially of grave significance and should be managed with great care. The gradual development of moderate anemia in those instances in which the course of the illness appears to be favorably influenced by the use of sulfanilamide is not a definite indication for the withdrawal of the drug; at times it may be wise to combat the lack of red blood cells by transfusion with whole blood, meanwhile continuing therapy with sulfanilamide.

Comment.—Six cases of acute pyelonephritis without a previous history of infection of the urinary tract were studied. In 2, the administra-

tion of sulfanilamide after the subsidence of the initial acute phase of the disease was followed by sterilization and clearing of the urine. In 2, the drug was given during the height of the illness and a dramatic clinical improvement, with rapid fall of temperature and sterilization of the urine, occurred. In 1 case, clinical and bacteriologic relapse was immediately controlled by reexhibiting the drug; a second mild relapse, associated with the presence of Staph. albus in the urine, was not affected. Three patients were available for further studies and were found to be well, with sterile urines, after intervals of from one to six months.

Two additional cases presented important features. In both, very marked clinical improvement followed the exhibition of the drug during the acute stage of the disease, with a definite reduction in the number of bacteria in the urine but without their elimination. In 1 case, a second course of the drug sterilized the urine promptly, although adequate mandelic acid therapy had previously failed to accomplish this result. It is impossible to assess exactly the effect of sulfanilamide on the outcome in this case; but it does seem definite that the drug favorably altered the course of the acute illness, and that later it was of great assistance in the eventual eradication of infection in the kidneys and in clearing the urine of bacteria. The fact that the blood became sterile on culture should not be interpreted as a definite effect of the drug, since such bacteremias are notoriously transient.[8]

The influence of the drug in the last case is impossible to evaluate. Clinical improvement and reduction of the total bacilluria accompanied the use of the drug but the blood culture remained positive. The result of its unfortunate withdrawal may suggest that had it been used continuously a favorable outcome would have been possible, but in the light of the observations at autopsy this is unlikely. Certainly infection of the kidneys by the colon bacillus may be expected to be so extensive or so complicated by various factors that death will ensue regardless of the type of therapy instituted.

Group 3. Acute Exacerbation of Chronic Infections of the Urinary Tract.—Cases 10 and 11 are examples of exacerbations of long-standing chronic cystitis with other disease as a complicating factor. The administration of sulfanilamide in these instances failed to sterilize the urine and was followed by symptomatic improvement in the second case only. In the latter the patient when seen one year later had been well, but his pyuria and bacilluria persisted.

The effect of this drug in cases of acute pyelonephritis following previous chronic infections is illustrated by cases 12, 13 and 14. The first

8. Keefer, C. S., and Felty, A. R.: Bacillus Coli Sepsis: Clinical Study of Twenty-Eight Cases of Blood Stream Infection by Colon Bacillus, J. A. M. A. **82**:1430 (May 3) 1924.

case it that of a young woman who had suffered from subacute to chronic cystitis for four years and who was admitted to the hospital with a severe recurrent infection of the kidneys, which subsided rapidly. Sulfanilamide therapy directed at the residual bacilluria and pyuria failed to sterilize the urine, although the patient became clinically well.

Case 13 is that of a young woman with decompensated rheumatic heart disease and chronic pyelonephritis of several years' duration. An acute exacerbation developed in the hospital and failed to respond to the usual therapeutic measures. A course of sulfanilamide, given by mouth, was instituted. Because of the depressed renal function (the standard urea clearance was only 30 per cent of normal) the concentration of the drug in the blood rose rapidly, and medication was stopped after four days. The concentration of sulfanilamide in the urine was high, and marked relief of all symptoms and sterilization of the urine took place. One year later she was found to have bacilluria and to suffer from frequent attacks of pain in the flanks, with fever.

The next case in table 1 (case 14) is that of a man, 27 years of age, who had a history of recurrent attacks of cystitis and pyelonephritis dating from childhood. He was severely ill on admission, with pain in the flank, fever, bacilluria and pyuria. All of these symptoms were readily controlled within a few days after exhibition of the drug, although bacteria continued to be present in the urine in small numbers. He was well when discharged, but he returned within two weeks in a relapse identical with the previous attack. Again the institution of sulfanilamide therapy was followed by rapid clinical improvement and sterilization of the urine. Adequate doses of mandelic acid were given for two weeks. When the patient was seen three months later, he was well and his urine was normal.

The following report presents in greater detail the course of the illness in a patient who suffered repeated attacks of infection in the right kidney.

Case 17.—A young woman was admitted to the hospital in November 1937 suffering from chills, fever, pain in the abdomen and the right flank and dysuria. The urine showed bacilli and pus. There was a history of several similar episodes. Since rest, the administration of fluids in large volume and an adequate trial of therapy with mandelic acid failed to clear the urine, and since retrograde pyelography revealed abnormal movement of the right kidney, with dilatation of the renal pelvis, right nephropexy was performed.

Convalescence was uneventful, but the patient was readmitted to the medical wards with a clinical picture identical with that on her previous entry. The course of her illness after that time, with pertinent data, is illustrated in chart 4. She improved rapidly on a regimen of rest and administration of large volumes of fluids. Three grams of sulfanilamide per day were given by mouth in two courses, and the bacilluria and pyuria rapidly disappeared. Organisms and cells reappeared in the urine promptly on the withdrawal of medication, and during

the second attack clinical relapse also was observed. At this time the urine was acidified and 12 Gm. of calcium mandelate was given daily for five weeks. Moderate pyuria and bacilluria continued. The patient was discharged, only to return in three weeks with complaints similar to those on her previous entries.

A trial of very large doses of sulfanilamide was considered advisable at this time; so 8 Gm. was given daily for fifteen days. The fluid output was limited to 1,500 cc.; a high concentration of the drug in the urine and blood, a return of the urine to normal and clinical improvement were thus attained. There was no reaction to the drug except slight headache. One week after withdrawal of sulfanilamide large numbers of bacteria and cells were to be found in the urine, although the patient felt well. Thirteen weeks later she was reexamined. The renal function was normal and the pyuria was minimal, but organisms could be

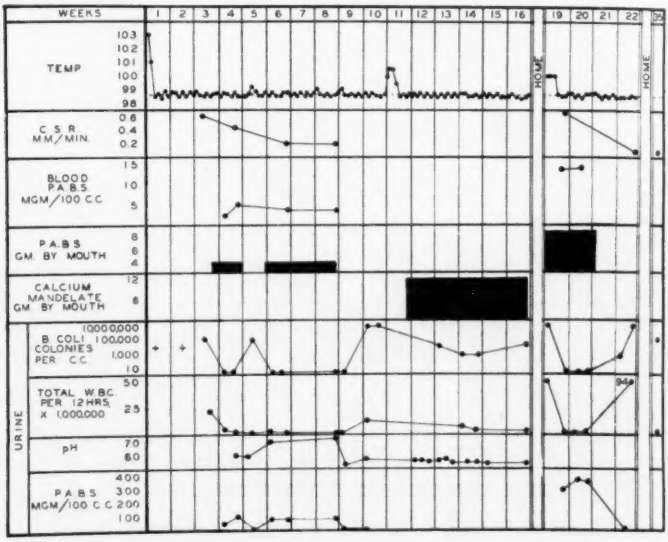

Chart 4.—Course of events in case 17.

isolated from the urine and she suffered frequent mild attacks of pain in the right flank.

This case illustrates the ease with which the evidences of disease may be eliminated in a patient who suffers from repeated attacks of urinary tract infection and the difficulty of bringing about a permanent cure by the use of sulfanilamide. It is also of interest and importance that two courses of calcium mandelate, under excellent control, failed entirely to eliminate bacteria from the urine.

Obstruction of the right ureter, of unknown cause, was undoubtedly the underlying process responsible for the continuing difficulty in this patient, but it is impossible to determine whether her repeated episodes

were the result of exacerbations of persisting chronic infection or of reinfections in a kidney more than normally susceptible to disease. The return of the excretion of white cells and of the sedimentation rate to within normal limits suggests, but in no sense proves, the latter hypothesis.

Comment.—Sulfanilamide failed to sterilize the urine in 3 cases of patients suffering acute exacerbations of chronic urinary tract infections, although the dosage and the concentration of the drug in blood and urine were similar to those in other cases in this study. In 3 other cases bacteria disappeared from the urine; but they were known to have reappeared in 2, and in the third mandelic acid was also used to effect a more permanent result. In 2 instances clinical relapse was also observed on one or more occasions. Treatment with sulfanilamide was followed in every case but 1 by rapid and striking clinical improvement, both in the initial phase and in relapse.

It is well known that a history of repeated infection of the urinary tract militates against the possibility of eventual permanent cure, as relapse and reinfection are notoriously common regardless of the methods of therapy used. These data suggest that, in so far as sulfanilamide is concerned, initial sterilization of the urinary passages may also be more difficult than in cases without such a history and, as is to be expected, the final results may not be wholly satisfactory.

Group 4. Marked Congenital Abnormality of the Urinary Passages.—One case in this classification, that of a young man admitted to the hospital in the acute phase of a very severe pyelonephritis, has been studied. Hypospadias was present, and retrograde pyelography revealed marked congenital abnormalities, with dilatation of the right pelvis and rotation of the left kidney; but there was no history of any previous acute episode. The administration of sulfanilamide was begun on the first day in the hospital; there was a rapid return of the temperature to normal, the urine was sterile within five days and the patient was discharged, well. He has not been seen since that time.

Comment.—Sulfanilamide was effective in relieving the symptoms and sterilizing the urine of a patient with marked congenital abnormalities of the urinary tract

CRITERIA OF CURE

It became evident early in this study that in certain instances the urine was very easily sterilized and pyuria markedly reduced after the oral administration of sulfanilamide. A few simple tests were then applied to a group of patients to determine whether such tests could be utilized as measures of the adequacy of therapy and permanence of cure. The procedures thought to be of the greatest potential value were determination of the sedimentation rate of the erythrocytes by the method of

Rourke and Ernstene, and estimation of the twelve hour excretion of white cells in the urine, by the method of Addis. The sedimentation rate is well established as a measure of tissue destruction within the body,[9] and the disappearance of pyuria has been used for many years as a criterion of healing of infections of the urinary tract. The results of these studies are summarized in table 2.

The sedimentation rate of the erythrocytes was measured in 6 patients at the completion of a course of therapy with sulfanilamide and was found to be within the normal limits of 0.35 mm. per minute in every instance. It had been elevated previously in all instances in which the determination was made during the acute illness. Two patients had remained well for intervals of seven and forty-five days; 2 had suffered attacks of acute

TABLE 2.—*Evaluation of Sedimentation Rate of Blood and Excretion of Leukocytes in Urine as Criteria of Results of Treatment*

	Sedimentation Rate, Mm. per Min.		No. White Blood Cells in Urine per 12 Hours			
	Before Treatment	After Treatment	Before Treatment, Million	After Treatment, Million	Follow-Up	
Case					Days	Results
1	....	....	450,000,000	13,000,000	30	Well; urine sterile
6	....	....	21,000,000	2,600,000	180	Well; urine sterile
7	1.60	0.35	.....	.....	45	Well; urine sterile
8	0.71	0.20	74,000,000	3,000,000	5	Mild cystitis
9	1.60	0.15	15,000,000	1,500,000	7	Well; urine sterile
13	....	....	450,000,000	3,000,000	180	Innumerable B. coli in urine
14	....	0.20	.....	7,500,000	14	Severe acute relapse
15	0.65	0.27	64,500,000	4,000,000	45	Acute cystitis
			1,200,000,000	5,000,000	120	Well; urine sterile
17	0.59	0.25	18,000,000	500,000	30	Relapse
	0.98	0.10	45,000,000	200,000	5	Relapse

cystitis, and 2 had severe clinical and bacteriologic relapse in the course of an acute pyelonephritis.

The excretion of white blood cells was studied in 8 patients. In 5 it was found to be within the normal limit of 3,000,000 cells per twelve hours. Of these, 2 were still well when last seen, in 1 cystitis had developed and 2 had suffered frank clinical and bacteriologic relapse, similar to the initial infection. Of those with abnormal excretion of cells, 1 has remained well, 1 has had a very severe cystitis and in 1 a very severe pyelonephritis developed within fourteen days after he left the hospital.

Case 17 is of interest because results of both tests were normal on two occasions after the exhibition of sulfanilamide, yet severe active infection of the kidney developed after withdrawal of the drug on each occasion, once within thirty and once within five days.

9. Ham, T. H., and Curtis, F.: Plasma Fibrinogen Response in Man, Medicine **17**:413, 1938.

Comment.—It is possible to conclude from these results that the disappearance of all signs of infection from the urinary passages, as evidenced by the return of the sedimentation rate and excretion of white cells to normal, does not guarantee a permanent cure of the disease, nor can these tests be used to determine effectively the optimum time for the cessation of therapy.

TOXIC EFFECTS OF SULFANILAMIDE

Minor toxic effects of the administration of sulfanilamide—cyanosis, headache, anorexia and malaise—have been repeatedly reported and were noted in nearly every case during the course of this study. In nearly all of the patients who were treated during the acute phase of their infection a slowly progressing anemia developed, without jaundice, with red blood cell counts falling to approximately 3,500,000 and hemoglobin contents to 65 per cent (Sahli). Several of these patients received the drug for prolonged periods and in comparable doses later, after the febrile period had passed, either without progression of the anemia or, if the blood had returned to normal, without its redevelopment. This would suggest that the presence of an acute febrile illness is in part responsible for the development of this complication. In certain instances, if the anemia seemed alarming, transfusions of whole blood were given and the use of the drug was continued. In others the diminution of red cells seemed to cease spontaneously at a certain level. In a third group the medication was withdrawn.

In 1 case a marked apathy and malaise was noted but none of the other complications reported by other authors were observed.

FACTORS INFLUENCING THE CLINICAL RESULTS

It is evident from the clinical results outlined previously that great differences exist in regard to the ease with which infections of the urinary tract can be initially eradicated and to the permanence of the eventual cure, for those patients who had previous histories of similar episodes were more difficult to relieve initially and to maintain in a state of health.

It is important to determine whether there are differences in the treatment of these patients or demonstrable factors in the patients themselves to account for these variations. The clinical facts have been examined with this in mind, and no striking differences between these patients have been demonstrated. All received similar basic treatment, with restricted activity and the administration of large volumes of fluid. The urinary output was recorded; the average was from 2,500 to 3,500 cc. per twenty-four hour period in each case. The dosage of sulfanilamide varied from 2 to 8 Gm., the usual amount being 3 Gm. per twenty-four hour period, in divided doses. The maximum observed concentrations of the unacetyl-

ated drug were from 2.5 to 13.7 mg. per hundred cubic centimeters in the blood and from 23.0 to 363.8 mg. in the urine. Medication was continued for from four to thirty-five days, but it is impossible to correlate the variation in time with any essential differences among the various groups. Naturally, it is true that the patients with more refractory infections received larger doses, attained higher levels of the drug in the blood and urine and were maintained on treatment for longer periods of time than those in whom a satisfactory result was obtained easily.

As Long [10] has suggested, larger doses and higher concentrations of the drug in the body fluids might have effected a sterilization of the urine in those cases in which this result was not obtained. In one case in which the medication was irregular this almost certainly was true. Nevertheless, amounts of the drug effective in some cases were ineffective in others, and in 2 instances large doses and high levels easily sterilized the urine but relapse occurred almost at once after withdrawal of the drug.

Physically the individual patients presented no striking differences except for the presence of pregnancy in one group, congenital malformation of the urinary passages in another, Hodgkin's disease in 1 patient, and diabetes mellitus in another. Retrograde pyelograms were taken regularly only when the infection was refractory to treatment, but they were approximately normal in every instance except cases 9 and 17.

In the light of these facts—that certain persons suffering from infections of the urinary passages present a disease state which is difficult both to control initially and to eliminate entirely by the use of sulfanilamide, and that striking differences either in therapeutic regimen or in the patients themselves are absent—a third possibility was suggested. This was that there might be a marked difference in the sensitivity of the various strains of infecting organisms to the drug, and this hypothesis was tested in vitro.

STUDIES ON THE COLON BACILLUS IN VITRO

Seven strains of Bacillus coli recovered from the patients previously described in this report were studied in vitro to determine whether there might be demonstrable individual differences in the organisms which made them less susceptible to the action of sulfanilamide. It was also desirable to know the minimal concentration of the drug that would cause maximum bacteriostasis. Long [10] has noted differences in the sensitivity of various strains, but he has maintained that if large doses of the drug are given and a high concentration of the drug in the urine is obtained better clinical results will follow in those instances in which refractory strains have been present in the urine.

10. Long, P. H., and Bliss, E.: Observations on the Mode of Action and Clinical Use of Sulfanilamide in Urinary Tract Infections, South. M. J. **31**:308, 1938.

Methods.—The organisms were grown for eighteen hours in ordinary veal infusion broth and diluted in tenfold steps in the medium to be studied, since Mellon [11] reported greater activity of the drug when diluent and test substance were urine. Agar pour plates were made with 1 cc. amounts of the various dilutions before and after a twenty-four hour period in the incubator, to obtain initial counts of the organisms and to determine the effect of the drug. Preliminary studies had revealed that the amount of sulfanilamide transferred to the plate with the medium would not affect the growth of the colon bacillus.

The urine used in certain instances was passed through a Berkefeld filter to insure sterility. Sulfanilamide was added in suitable amounts from an 0.8 per cent solution. When mandelic acid was used, it was added to the urine in the crystalline form, by weight.

Since Helmholz had suggested that the action of the drug in vitro is greater if the medium is alkaline, many of the tests were performed at various levels of p_H, from 5.5 to 8. In those involving mandelic acid, the urine was adjusted to p_H 5.5 after the addition of the acid.

Effect of Sulfanilamide in Veal Infusion.—A preliminary study of 4 strains of B. coli, grown and diluted in ordinary broth at p_H levels of 5.5, 6.5, 7.5, and 8 and at concentrations of sulfanilamide of 40, 80, and 160 mg. per hundred cubic centimeters, revealed no bacteriostatic or bactericidal effect of the drug in 3 instances and very slight inhibition of growth in the fourth.

Effect of Sulfanilamide in Urine.—After demonstrating the apparent inactivity of the drug against 4 strains of B. coli in broth, we studied the same strains in urine of varying p_H and at different concentrations of the drug, to evaluate the possible effects of these two variables. The results are presented diagrammatically in chart 5.

Strains 1 and 2 were most susceptible to the action of the drug, and very marked bactericidal action was demonstrated. As many as 100,000 organisms of strain 1 were killed and as many as 10,000 of strain 2. The tests with strains 3 and 4 revealed very clearly the bacteriostatic activity of the drug, but only a few organisms were killed.

It is of great interest that no significant effect of p_H was demonstrated and that with these strains a very much greater increase in the effectiveness of the drug was noticed when its concentration was raised from 40 to 80 mg. than when it was raised from 80 to 160 mg. The latter increase in concentration failed in every instance to produce a significant increase in either bacteriostatic or bactericidal effects. With strains 3 and 4, even when the concentration of the drug was raised to 320 mg., no additional inhibition of growth was observed.

Since it was possible that the urine might be more bacteriostatic than the amount of uncombined sulfanilamide present would suggest, owing to

11. Mellon, R. R., and Shinn, L. E.: Potentiating Influence of Urine on Sulfanilamide's Bacteriostatic Effect on E. Coli in Vitro, Proc. Soc. Exper. Biol. & Med. **37**:331, 1937.

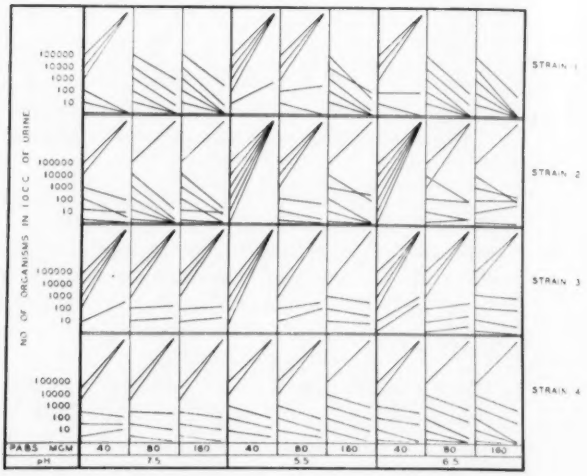

Chart 5.—Effect of sulfanilamide, in varying concentrations and at different p_H, on 4 strains of colon bacillus isolated from patients with infections of the urinary tract. Strain 1 was isolated from the patient in case 3; strain 2, from a patient not discussed in this paper; strain 3, case 17; strain 4, case 8.

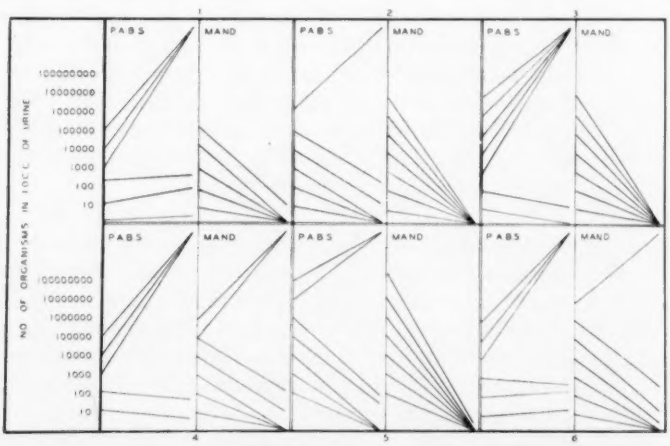

Chart 6.—Comparative effects of sulfanilamide and mandelic acid on 6 different strains of colon bacillus. The concentration of sulfanilamide was 160 mg. per hundred cubic centimeters of urine, and that of mandelic acid was 1000 mg.; the p_H was 5.5. Strain 1 was isolated from the patient in case 8; strain 2, case 1; strain 3, case 15; strain 4, case 13; strain 5, case 3; strain 6, case 17.

the presence of an equal amount of the acetylated compound, these same strains were tested in two samples of urine from a patient to whom the drug had been administered by mouth. One specimen contained 81.0 and 37.8 mg., per hundred cubic centimeters of the combined and the free form, respectively; the other, 150.0 and 93.6 mg., respectively. Each strain was studied at different levels of p_H, and in every instance the results were exactly comparable to those of the previous tests; the entire activity of the drug was apparently in its unacetylated form, as had been previously reported.[12]

Six strains of B. coli isolated from patients under observation were studied in urine with the concentration of sulfanilamide 160 mg. and the p_H 6.5 and, as a comparison, in urine with the concentration of mandelic acid 1 per cent and the p_H 5.5. The results of these experiments are depicted graphically in chart 6.

Sulfanilamide had marked bactericidal effects only on strains 2 and 5. No marked differences were observed among the other 4 strains; the demonstrable effect was moderate bacteriostasis.

Clinically, the urine in 5 of these patients was sterilized with ease, the concentration of the drug in the urine being less than 100 mg. in every instance. In the sixth (case 3) a very great reduction in the total number of organisms excreted took place at a time when the urinary concentration was 23.0 mg.

Two of the strains under discussion, 4 and 6, were isolated from patients in whom unsatisfactory clinical results were obtained, in the sense that relapse occurred in each. Yet neither of these organisms in vitro appeared to be more refractory than the others studied.

The studies conducted with mandelic acid, under conditions comparable to those existing in the urinary passages, are also very striking. Chart 6 shows that with every strain this agent was much more effectively bactericidal than sulfanilamide, since from 100,000 to 1,000,000 organisms were killed in every instance, with some variation among the strains.

Clinically, however, this drug was administered to 2 patients (cases 15 and 17), under controlled conditions, with only minimal reduction of the number of organisms in the urine. Subsequent exhibition of sulfanilamide readily sterilized the urine in these persons. This is suggestive evidence that the modes of action of sulfanilamide and mandelic acid are different and also that in vitro studies are liable to give a false impression as to the relative values of urinary antiseptics.

Comment.—It has been possible to demonstrate certain facts by these studies on the colon bacillus in vitro. Sulfanilamide is bacteriostatic or bactericidal for this organism, most markedly so when the concentration

12. Marshall, E. K.: Bacterial Chemotherapy: The Pharmacology of Sulfanilamide, Physiol. Rev. **19**:240, 1939.

of the drug is approximately 80 mg. or more per hundred cubic centimeters. Increase of concentration above this level does not strikingly improve the action of the drug. No effect of p_H on its activity was demonstrable. Definite differences exist in the relative sensitivities of various strains of B. coli to the drug; but clinical sterilization of the urine occurs at levels which are only bacteriostatic in vitro and no correlation was observed between the in vitro and the clinical results in those instances in which unfavorable therapeutic effects had been observed.

Mandelic acid is much more actively bactericidal than sulfanilamide in vitro, yet in these studies it was much less satisfactory for sterilizing the urine in vivo.

GENERAL COMMENT

To understand the action of urinary antiseptics it is necessary to review some aspects of both the pathology of pyelonephritis and the mechanisms by which infection may reach the kidney.

Pathologic investigation of this type of renal infection has shown[13] that there is primarily an involvement of the lymphatic system of the organ. In many instances inflammation and necrosis of the epithelium of the pelvis and calices occurs, but, in addition, there is always widespread inflammation between the tubules and glomeruli, with cellular infiltration and very often small abscesses in these areas, from which bacteria may be recovered. Healing is regularly accompanied by scarring and contraction of the kidney.

The manner in which the infecting organism is able to reach the kidney and the mechanisms responsible for maintaining the disease have long been the subject of debate. It is generally agreed that obstruction to the free flow of urine predisposes this organ to infection. The principal source of disagreement is the question of whether the organisms reach the kidney by way of the blood stream or ascend from the lower urinary passages. Such arguments are highly academic, especially in the light of recent experimental evidence which indicates that in the presence of urinary obstruction intravenous or intraureteral injection of the colon bacillus in the rabbit will produce renal lesions practically identical with those of human pyelonephritis.[14]

In summary, then, pyelonephritis is an infectious process which involves the entire kidney rather than the superficial tissues of the pelvis, and to which there is a predisposition in the presence of obstruction to the free flow of urine. It is fair to assume that most of the patients described in this report suffered from disease of this nature.

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13. Weiss, S., and Parker, F., Jr.: Pyelonephritis: Its Relation to Vascular Lesions and to Arterial Hypertension, Medicine **18**:221, 1939.

14. Mallory, K.: Personal communication to the authors.

In the light of these facts, it is obvious that to regard the infected urinary passage as a container of urine, to be sterilized by the excretion into it of a bactericidal agent, is too superficial, since much of the infectious process lies deep in the renal tissue, far removed from the urine. One might postulate that the drug-containing urine is reabsorbed by the renal lymphatic system, but this is a somewhat unlikely hypothesis. The dramatic results of the administration of sulfanilamide, which frequently include sterilization of the urine in spite of only bacteriostatic or moderately bactericidal effects in vitro suggest that the action of the drug in the patient is more complex than in the test tube.

It is certainly true that the infection in the parenchyma of the kidney must be cleared by the same cellular and immune mechanisms responsible for the healing of inflammatory processes elsewhere in the body. The effectiveness of the therapeutic agent here is limited to that degree of bacteriostasis which it is able to exert in those concentrations in which it it brought to the tissues by the blood stream.

In view of these observations, it seems likely that an agent which in vitro exerts marked bacteriostasis or bactericidal effects against the organisms responsible for an infection of the urinary passages has a threefold mode of action in the infected kidney.

First, the presence of the agent in the urine inhibits the multiplication of the organism in the tubules, pelvis, ureter and bladder, and may destroy it. It is possible that those membranes in direct contact with the urine may absorb a sufficient amount of the drug for this effect to occur in their most superficial layers. The direct result of this action will be decreased production of toxin in the urinary tract, with consequent reduction of superficial inflammation, congestion and edema and, in turn, resultant relief of symptoms and decrease in obstruction to the urinary flow. Water diuresis, long known to affect favorably the course of these infections, acts in a similar but less dramatic manner by washing away the organisms from these areas.

Second, the elimination of obstruction and the inhibition of multiplication of the bacteria in the urine must markedly reduce the possibility of the reinfection which undoubtedly occurs in the deeper renal tissues when the tubules are engorged and the organisms are multiplying freely.

Third, depending on the possible relationship of the effect of the drug to its concentration in the blood, there may be direct action on the organisms in the deeper tissues, slowing their multiplication and permitting the usual clearing mechanisms to operate more effectively. This action may be important in its effect on the colon bacillus, since these organisms are usually so weakly invasive that even a very slight reduction in the rate of

increase of the bacteria might be adequate to enable the tissues to eliminate them.

It is, then, probable that final recovery from infections of the kidney results from the activity of the immunogenic mechanism of the body, which may be aided by certain chemical agents. In support of this theory are the facts that most acute renal infections are self limited and that healing is complete, in the absence of obstruction, even though no special therapy is instituted. Relapse in the presence of obstruction may very well be due to repeated reinfection. Chronic infections without demonstrable obstruction, such as are described in this paper, are extremely difficult to relieve with any drug; this fact suggests that the bacteria continue to remain viable and multiply in the tissues because of some unknown defect in the mechanism by which the body usually removes infecting agents.

From the study of the sensitivity of different strains of B. coli which were isolated from the urine of patients with pyelonephritis the following facts emerged: When the bacteria were incubated at different p_H levels in veal infusion broth which contained varying concentrations of sulfanilamide it was not possible to demonstrate that the drug had either a bacteriostatic or a bactericidal effect. However, when the same strains were studied in sterile urine which contained sulfanilamide the results were different; in all instances there was bacteriostasis and on 2 strains the drug had definite bactericidal effects. It was of interest that varying the p_H of the urine seemed to produce no significant difference in the action of sulfanilamide. The concentration of the drug, on the other hand, was of the highest importance. The most striking increase in the efficacy of the drug occurred when the concentration was increased from 40 to 80 mg.; there was little demonstrable increase in the action of the drug when higher concentrations were used. The study also confirmed the observation of other workers that in samples of urine which contain both the free and the acetylated form of sulfanilamide the free form is the active principle.

It was of interest to compare the results in vitro with those in vivo. It was found that in 5 of the 6 cases in which bacteria were cultured and tested in vitro, administration of sulfanilamide in vivo sterilized the urine; the concentration of the drug in the urine was less than 100 mg. in every case. In the sixth case, a great reduction in the total number of organisms excreted took place at a time when the concentration of the drug in the urine was only 23 mg. These observations indicate that in the test tube it is possible to show bactericidal effects of sulfanilamide on only a few strains of B. coli, and on other strains the effect is merely bacteriostatic. On the other hand, when the drug is given to patients it often

prevents the growth of organisms in the urine. This suggests that the action in the body is different from that in vitro and that there are extra-pharmaceutic factors to account for this difference.

When the effects of mandelic acid and of sulfanilamide on the same strains of B. coli in vitro were compared, it was found that mandelic acid in 1 per cent concentration at a p_H of 5.5 was a much more effective bactericidal agent than sulfanilamide, since from 100,000 to 1,000,000 organisms were killed in every instance. There was some variation in resistance among the strains. However, when mandelic acid was given to patients it brought about only a minimal reduction of the number of organisms in the urine. Here the evidence again suggests that the mode of action of the drug is different in vivo and in vitro, and that in vitro studies are liable to give an erroneous impression as to the relative values of urinary antiseptics.

SUMMARY

A study of treatment with sulfanilamide in 17 cases of infection of the urinary tract due to Bacillus coli is presented. Clinical improvement and sterilization of the urine were easily accomplished in most instances; the best results were obtained in those cases in which there was no previous history of infection of the urinary tract and in those in which the infection was associated with pregnancy. If evidence of chronic infection of the urinary passages was present the urine was more difficult to sterilize, and clinical and bacteriologic relapse frequently occurred.

The urine usually could be sterilized by the administration of 2 to 5 Gm. of sulfanilamide in twenty-four hours by mouth; this dose resulted in concentrations of from 23.0 to 139.0 mg. of the drug per hundred cubic centimeters of urine. No definite correlation was demonstrable between the dose of sulfanilamide, its concentration in the urine and the permanence of cure. The return to normal of the number of formed elements excreted in the urine and of the sedimentation rate could not be regarded as indicative of permanent eradication of infection from the urinary tract.

The usual toxic symptoms associated with the administration of sulfanilamide were observed. Anemia regularly appeared when the drug was exhibited in the presence of fever but usually failed to recur when the drug was administered in the absence of fever.

Seven strains of B. coli isolated from the urines of these patients were studied in vitro. Sulfanilamide had marked bacteriostatic and, in certain instances, bactericidal effects on the bacteria; there were great differences in sensitivity to the drug between the various strains. Optimal bacteriostasis was obtained with concentrations of more than 80 mg. of sulfanilamide per hundred cubic centimeters of urine. To increase its

concentration above 160 mg. did not significantly increase the drug's effectiveness. The p_H of the urine did not affect the activity of the drug in vitro.

No correlation was demonstrated between the activity of sulfanilamide in vitro and that in vivo. Mandelic acid in vitro was markedly bacteriostatic for all strains, but in vivo it was not as effective as sulfanilamide in sterilizing the urine.

The mode of action of urinary antiseptics in relation to the pathologic process in infections of the urinary tract is considered.

BACTERIAL ENDOCARDITIS SUPERIMPOSED ON SYPHILITIC AORTIC VALVULITIS

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Though syphilitic aortic valvulitis and vegetative bacterial endocarditis are well established separate clinicopathologic entities, the concomitant occurrence of the two processes on the same valve has been regarded as extremely rare,[1] and relatively little has been written on this subject. In 1920 Libman [2] remarked on the infrequency with which bacterial endocarditis attacked valves previously altered by a syphilitic process. Thayer's [3] excellent monograph on infective endocarditis gives the impression that the cases of simultaneous syphilitic and bacterial aortic valvular involvement mentioned (i. e., 4 certain cases and 2 doubtful ones) are admitted reluctantly and with a skepticism that such combinations occur. Blumer,[4] Gross and Fried [5] and Levine [6] likewise merely mention 1 case each but give no further details. Review of the literature has yielded only 11 proved cases.[7] Despite this paucity

From the Department of Pathology and the Department of Medicine, Baltimore City Hospitals.

Read by title before the American Society for Clinical Investigation, Atlantic City, N. J., May 1, 1939.

1. (*a*) MacCallum, W. G.: A Text-Book of Pathology, ed. 6, Philadelphia, W. B. Saunders Company, 1936, pp. 695 and 701. (*b*) White, P. D.: Heart Disease, New York, The Macmillan Company, 1935, p. 365.

2. Libman, E., in discussion on Horder, T.: Discussion on the Clinical Significance and Course of Subacute Bacterial Endocarditis, Brit. M. J. **2**:304 (Aug. 28) 1920.

3. Thayer, W. S.: Studies on Bacterial (Infective) Endocarditis, Johns Hopkins Hosp. Rep. **22**:1, 1926.

4. Blumer, G.: Subacute Bacterial Endocarditis, Medicine **2**:105 (May) 1923.

5. Gross, L., and Fried, B. N.: Role Played by Rheumatic Fever in Implantations of Bacterial Endocarditis, Am. J. Path. **13**:769 (Sept.) 1937.

6. Levine, S. A.: Clinical Heart Disease, ed. 2, Philadelphia, W. B. Saunders Company, 1936, p. 192.

7. (*a*) Kastner, A.: Ueber Endocarditis lenta, Deutsches Arch. f. klin. Med. **126**:370, 1918. (*b*) Briggs, L. H.: Bacterial Endocarditis as a Sequel to Syphilitic

(Footnote continued on next page)

of material, we have come to think that bacterial endocarditis engrafted on syphilitic aortic valves, though not nearly as common as on rheumatic valves, occurs more frequently than has heretofore been recognized. In this connection a brief summary of the chronologic developments concerning the knowledge of rheumatic and syphilitic heart diseases will be presented, since the much earlier recognition of the pathologic changes in rheumatic heart disease and the greater frequency of bacterial endocarditis on rheumatic valves than on syphilitic valves have no doubt overshadowed the incidence of superimposed bacterial endocarditis in other valvular states.

REVIEW OF THE LITERATURE

The first record of clinical and pathologic observations in a case of bacterial endocarditis was made by Lancisi in 1707,[8] and a little more than one hundred years later the characteristic lesions of acute rheumatic valvulitis were described.[9] A differentiation between these two valvular conditions was first attempted in 1851 by Ormerod,[10] and in 1885 Osler[11] observed that valves which were the seat of "malignant endocarditis" frequently showed signs of previous damage. From the early part of the twentieth century to the present time a steady stream

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Valve Defects, Am. J. M. Sc. **164**:275 (Aug.) 1922. (*c*) Pineles, F.: Aortenlues und Endocarditis lenta, Med. Klin. **22**:444 (March 19) 1926. (*d*) Cade, A.: Endocardite infectieuse à marche lente greffée sur une aortite syphilitique, Lyon méd. **139**:731 (June 19) 1927. (*e*) Schnabel, T. G., and Leivy, F. E.: Cardiac Patients with Other Associated Diseases, M. Clin. North America **15**:325 (Sept.) 1931. (*f*) Craven, E. B.: Syphilitic Aortic Endocarditis and Superimposed Bacterial (Streptococcus Viridans) Endocarditis, Am. J. Path. **8**:81 (Jan.) 1932. (*g*) Raybaud, A.; Jouve, A., and Farnarier, G.: Maladie de Jaccoud-Osler greffée sur une aortite chronique syphilitique, Bull. et mém. Soc. méd. d. hôp. de Paris **51**: 136 (Feb. 4) 1935. (*h*) McMillan, R. L., and Wilbur, E. L.: Staphylococcic Endocarditis Superimposed on Syphilitic Aortic Endocarditis, J. A. M. A. **109**:1194 (Oct. 9) 1937. (*i*) Smith, F. J.: Co-Existence of Syphilis of the Aorta and Bacterial Endocarditis, Internat. Clin. **2**:1 (June) 1937. (*j*) Martin, H. E., and Adams, W. L., Jr.: Bacterial Endocarditis Superimposed on Syphilitic Aortitis and Valvulitis: Clinicopathological Study with Five Case Reports, Am. Heart J. **16**:714 (Dec.) 1938.

8. Lancisi, cited by Perry, C. B.: Bacterial Endocarditis, Bristol, John Wright & Sons, Ltd., 1936.

9. Wells, W. C.: On Rheumatism of the Heart, Tr. Soc. Improve. M. & Chir. Knowl. **3**:373, 1812. Corvisart, J. N.: A Treatise on the Diseases and Organic Lesions of the Heart and Great Vessels, translated by C. H. Hebb, London, Underwood & Blacks, 1813.

10. Ormerod, E. L.: Gulstonian Lectures for 1851, London M. Gaz. **12**:529, 617 and 705, 1851.

11. Osler, W.: The Gulstonian Lectures on Malignant Endocarditis, Brit. M. J. **1**:467, 522 and 577, 1885.

of excellent work has appeared emphasizing strongly the "frequent association and etiologic relationship" of rheumatic valvular alterations and bacterial endocarditis.[12] Since the time of Paget,[13] bicuspid valves have often been described as being particularly disposed to implantation of bacterial vegetations.[14] More recently, Gross [15] has indicated his belief that even "most of the bicuspid valves seen in adults owe their deformity to a previous rheumatic process."

In sharp contrast to the developments concerning the knowledge of rheumatic heart disease and its frequent sequel, bacterial endocarditis, the progress in the field of cardiovascular syphilis has been slow and relatively recent, even though syphilis itself has been known since the epidemics which occurred in the fifteenth and sixteenth centuries. It remained for Francis H. Welch [16] to give the first accurate descriptions of syphilitic aortitis and valvulitis in 1875. The essential facts concerning the pathologic changes are embodied in his report. There are but few differences between Welch's early descriptions and those encountered today, and Osler [17] commented in 1909 that this report remains "the most important communication upon the subject in English." Unfortunately, however, Welch's work was soon forgotten, but in 1885, Döehle,[18] working in Heller's laboratories in Kiel, revived the interest in vascular syphilis by describing a typical case of aortitis, and in 1890 he published a very complete description of the microscopic changes. Opposition to both Döehle's and Heller's views was maintained, how-

12. Horder, T. J.: Infective Endocarditis, with an Analysis of One Hundred and Fifty Cases and with Special Reference to the Chronic Form of the Disease, Quart. J. Med. **2**:283, 1909. Libman, E.: A Study of the Endocardial Lesions of Subacute Bacterial Endocarditis, with Particular Reference to Healing or Healed Lesions, with Clinical Notes, Am. J. M. Sc. **144**:313, 1912. Combs, C. F.: Rheumatic Heart Disease, Baltimore, William Wood & Company, 1924. Swift, H. F.: The Heart in Infection, Am. Heart J. **3**:629 (Aug.) 1928. Davis, D., and Weiss, S.: Relation of Subacute and Acute Bacterial Endocarditis, New England J. Med. **208**:619, 1933.

13. Paget, J.: On Obstructions of the Branches of the Pulmonary Artery, Proc. Roy. Med.-Chir. Soc. **27**:162, 1844.

14. Osler, W.: The Bicuspid Condition of the Aortic Valves, Proc. A. Am. Physicians **1**:185, 1886. Lewis, T., and Grant, R. T.: Observations Relating to Subacute Infective Endocarditis, Heart **10**:21 (April) 1923.

15. Gross, L.: So-Called Congenital Bicuspid Aortic Valves, Arch. Path. **23**: 350 (March) 1937.

16. Welch, F. H.: On Aortic Aneurism in the Army and the Conditions Associated with It, Med.-Chir. Tr. **59**:59, 1876.

17. Osler, W.: The Schorstein Lecture on Syphilis and Aneurysm, Brit. M. J. **2**:1509, 1909.

18. Cited by Conner, L. A.: Development of Knowledge Concerning Role of Syphilis in Cardiovascular Disease (Frank Billings Lecture), J. A. M. A. **102**: 575 (Feb. 24) 1934.

ever, until the meeting of the German Pathological Society in 1903. To quote MacCallum [1a] (p. 695), "It was impressive and a revelation to listen . . . to the discussion by Chiari, Benda and Marchand, of the discovery of Döehle and Heller of the syphilitic nature of these changes, and particularly to realize the perfectly characteristic and peculiar appearance of the aorta so affected. Since then everyone has recognized it at a glance . . ." Confirmation of these observations was provided by Fränkel and Much [18] in 1908. They reported positive Wassermann reactions of the blood in 19 of 23 cases in which typical syphilitic mesaortitis was found at autopsy. As for the clinical diagnosis in cardiovascular syphilis, Curschmann [18] was probably the first to describe the tympanitic second aortic sound so frequently identified with syphilitic aortitis, although he did not realize it at the time. However, the clinical significance of this observation as well as the signs of aortic insufficiency were not generally appreciated until after the advent of the more universal acceptance of the associated pathologic changes.

To our best knowledge the first proved case of bacterial endocarditis superimposed on syphilitic aortic valvulitis was reported by Kastner [7a] in 1918. His patient, a 54 year old white man, had syphilis (the Wassermann reaction of the blood was positive), and he presented the typical clinical course of bacterial endocarditis. Examination at autopsy revealed syphilitic aortitis and aortic valvulitis with superimposed bacterial endocarditis. Blood cultures during life and at postmortem examination were sterile, but numerous organisms could be demonstrated on the valve by means of bacterial stains. In 1922 Briggs [7b] reported the case of a 35 year old man who on his first admission to the hospital had syphilis (the Wassermann reaction of the blood was positive and he had a penile scar) and typical aortic insufficiency. Through the fault of the patient little antisyphilitic therapy was given, and one year later he was readmitted, with signs of bacterial endocarditis. Repeated blood cultures showed growths of nonhemolytic streptococci. Postmortem examination revealed syphilitic aortitis and valvulitis with superimposed "acute verrucose endocarditis" and contact vegetations on the anterior mitral leaflet. In the third case, reported in 1926 by Pineles,[7c] a positive blood culture was made showing Streptococcus viridans, and autopsy showed syphilitic aortitis and valvulitis as well as bacterial endocarditis. Cade [7d] added a similar case in 1929, and Schnabel and Leivy [7e] in 1931 reported the fifth case. In 1932 Craven [7f] studied a case in which there was syphilitic aortitis with valvulitis. Postmortem cultures showing Streptococcus viridans were obtained from the blood and from the bacterial vegetations on the aortic cusps. There was no evidence or history of rheumatism. Raybaud, Jouve and Farnarier [7g]

in 1935 reported a case in which a "streptenterococcic" organism was isolated during life. The eighth case to be reported was that of McMillan and Wilbur [7h] in 1937. It is extremely interesting because the portal of entry was almost certainly suggested by the clinical history. The patient, a 47 year old white man, had a positive Wassermann reaction of the blood and through his own negligence was inadequately treated. Bouts of precordial pain from which he suffered were relieved by morphine, and soon the patient became addicted to the drug. In the last year of his life he administered the drug to himself intravenously, using "poorly sterilized tap water." On this, his last, readmission to the hospital, the clinical diagnoses were syphilitic aortitis with aneurysm formation and aortic insufficiency, and subacute glomerulonephritis. Bacterial endocarditis was suspected. At autopsy these diagnoses were confirmed, and a vegetative bacterial endocarditis was found on the aortic and mitral valves. A postmortem culture taken from the spleen showed a "pure growth of hemolytic Staphylococcus aureus." There was no evidence of rheumatic lesions on the mitral valve. The ninth case was reported by Smith [7i] in 1937. The patient was a 63 year old white man in whom septicemia developed in the course of an infection of the lower part of the urinary tract, a prostatic abscess. The Wassermann reaction of the blood was positive, and Staphylococcus albus was grown from material from the blood stream. In 1938, Martin and Adams [7j] reported 5 cases in which bacterial endocarditis was associated with syphilitic aortitis or valvulitis. Only 2 of their cases could be classified as ones in which bacterial endocarditis was superimposed on syphilitic valvulitis. The Wassermann reactions were positive in both cases, and a postmortem culture of the blood in 1 case showed a growth of Streptococcus viridans.

Our interest in this combination of maladies was aroused by the opportunity to observe 2 such cases during the past year. We were further stimulated by the fact that investigation of our protocols revealed the presence of 7 other proved cases which were similar. These 9 cases, provide the *raison d'être* for this study.

MATERIAL

In order to obtain cases which were unimpeachable, rigid criteria for their selection were imposed. In all the cases there were histories of syphilis, positive Wassermann reactions of the blood or, when the reactions were negative, histories of antisyphilitic treatment. In the autopsy records there were descriptions of the characteristic syphilitic changes, not only in the aorta but also in the sinuses of Valsalva and in the aortic valve cusps. In addition, the bacterial vegetations had to be accurately located and described, and complete descriptions given of the

valves other than the aortic to rule out especially the possibility of previous rheumatic valvular involvement. Sections taken for microscopic study included material from the aorta, the sinus of Valsalva, the aortic valve cusps and the vegetations. In this manner the syphilitic changes could be traced directly to the valve cusps on which the bacterial vegetations were superimposed. All the cases were restudied and fresh sections made. The bacteria and all the vegetations were stained by the method employed by Brown and Brenn;[19] in the sections of the aorta and the aortic valves the diminution of elastic tissue and medial interrup-

TABLE 1.—*Analysis of 4,921 Autopsies, Showing the Distribution of Various Valvular States as Well as Bacterial Endocarditis (Acute and Subacute) on Previously Injured and Normal Valves in Association with Syphilis* *

Type of Valvular Disease	Syphilitic	Rheumatic: With a Positive Wassermann Reaction of the Blood	Rheumatic: With Syphilitic Aortitis and Valvulitis	Rheumatic: Unassociated with Syphilis	Bicuspid	Normal: With Positive Wassermann Reaction	Normal: Without Positive Wassermann Reaction	Arteriosclerosis
Superimposed bacterial endocarditis (acute and subacute)	9 (3.3+%)	3‡ (1.6%)	4‡ (2.1%)	22 (11.7%)	7 (53.7%)	5‖	4‖	4‖
No bacterial endocarditis	258	23	4	132	6§	?	?	?
Totals	267† (99.9+%)	26 (13.8%)	8 (4.2%)	154 (81.9%)	13 (99.8+%)	4,453 (Total of Normal and Arterioscleorotic Valves)		
		(Total Rheumatic—188)						

* Each per cent stated is that part of the total in the given column.
† This figure represents 32.6 per cent of the cases of syphilitic aortitis (i. e. 818) or 20.4 per cent of all the cases of syphilis (i. e. 1,310) among the 4,921 cases analyzed.
‡ The bacterial vegetations were located on the rheumatic valve.
§ Five doubtful cases were not included.
‖ Since it was impossible to separate the normal and arteriosclerotic valves accurately, no definite totals are included here.

tions were demonstrated by Verhoeff's and Van Gieson's stains. Care was taken to exclude all cases in which it was thought that terminal bacterial invasion of the blood stream might have played a role—cases of so-called terminal bacterial endocarditis.

Among 8,700 autopsy protocols we were able to find complete records of 17 cases in which vegetative bacterial endocarditis was superimposed on syphilitic aortic valvulitis. Though we felt that all of the latter were bona fide examples, we were obliged to exclude 8 of them for lack of suitable material for microscopic study. Even if we had

19. Brown, J. H., and Brenn, L.: Method for Differential Staining of Gram-Positive and Gram-Negative Bacteria in Tissue Sections, Bull. Johns Hopkins Hosp. **48**:69 (Feb.) 1931.

been able to include these additional cases, the statistics about to be presented would have been altered only slightly, since the present series of cases is practically a mirror of the cases omitted. The 9 remaining cases which we have studied were selected in the last 4,921 consecutive routine autopsies. An analysis of the observations made in these autopsies, showing the occurrence of syphilitic and rheumatic valvular diseases and their various combinations, is to be found in table 1. The percentile distribution of 58 cases of bacterial endocarditis (acute and subacute) on previously injured and normal valves is shown in table 2.

For the sake of brevity, only 1 case is presented in detail, a case of subacute bacterial endocarditis. An analysis of the other cases as well as those abstracted from the literature is to be found in tables 3 and 4. In these tables our 9 cases are numbered 12 to 20, inclusive, and the report which follows is of case 17.

TABLE 2.—*Percentile Distribution of 58 Cases of Bacterial Endocarditis (Acute and Subacute) on Previously Injured and Normal Valves*

Syphilitic	Rheumatic	Bicuspid	Normal	Arterio-sclerotic	Total
15.5% (9)	50.0% (29)	12.07% (7)	15.5% (9)	6.92% (4)	99.9% (58)

REPORT OF A CASE

History.—N. I., a Negro aged 31, was admitted to the medical service of the Baltimore City Hospitals on Nov. 26, 1937, with complaints of shortness of breath and weakness. The family history was irrelevant. The patient had never had rheumatic fever. He was unable to date his syphilitic infection and had never had any antisyphilitic therapy. He had been in excellent health until the onset of his present illness. Five weeks prior to his admission to the hospital a chest cold developed. There was associated dyspnea, which became progressively worse. Four weeks prior to admission there was an onset of orthopnea, weakness, epigastric discomfort, and dependent edema. For three and one-half weeks before coming to the hospital he was confined to bed with the aforementioned symptoms. There were no chills or symptoms of fever.

Physical Examination.—The temperature was 99.4 F. (37.4 C.). The pulse rate was 100, the respiratory rate 22 and the blood pressure 130 systolic and 50 diastolic. The patient appeared in acute respiratory distress with Cheyne-Stokes breathing and generalized edema. He was well developed and well nourished. Only moderate cyanosis was present. The pupils reacted to light and in accommodation. There were signs of some congestive changes at the bases of both lungs. The heart was enlarged to the right and to the left, and a gallop rhythm was noted. There were no murmurs at the base, but a musical systolic murmur was present at the apex. The liver was felt and percussed 2 fingerbreadths below the right costal margin. The spleen was not palpated. Two days later the apical systolic murmur had disappeared and a diastolic murmur was noted over the aortic region. The pulse was of the Corrigan type. There was marked edema of the abdomen and both lower extremities.

TABLE 3.—*Tabulation of Essential Clinical Data on 20 Cases of Bacterial Endocarditis Superimposed on Syphilitic Aortic Valvulitis* *

	Case																		
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
Age	54	35	32	42	53	23	50	47	63	61	42	44	39	40	37	40	31	52	40	28
Sex	M	M	M	M	F	M	M	M	M	M	M	M	M	M	M	F	M	M	M	M
Race	W	—	W	W	W	B	W	W	W	W	B	B	B	B	B	B	B	W	B	B
Wassermann reaction of the blood†	+	+	+	+	+	+	0	+	+	+	+	+	+	+	+	0	+	0	+	+
Wassermann reaction of the spinal fluid	—	0	—	—	+	—	0	0	—	—	—	0	0	+	0	0	+	0	+	+
Duration of syphilis in years	8	15	—	19	34	4	—	29	?	46	26	?	?	12	?	?	?	?	8	?
Antisyphilitic therapy	—	+	—	—	0	+	+	+	0	0	+	0	0	+	0	+	0	+	0	0
History of rheumatic fever	—	0	—	0	0	0	0	0	0	0	0	0	0	0	0	0	0	—	0	0
Temperature‡	I	S	—	S	S C	0	0	0	S C	I	S R	S C	S I	0	S I	C	I	C	I	S R
Subjective sense of fever	0	+	0	+	+	0	0	+	+	0	+	+	0	0	0	0	0	0	0	0
Chills	0	+	0	+	+	0	0	+	+	0	+	+	0	0	0	0	0	0	0	0
Dyspnea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Joint pains	+	0	0	0	0	0	0	+	0	0	0	0	0	0	0	0	0	0	0	0
Embolic phenomena	0	+	—	0	+	—	+	0	0	+	0	0	+	0	+	0	0	+	0	0
Petechiae	+	+	—	0	0	—	0	0	0	0	0	0	+	0	+	0	0	+	+	0
Clubbed fingers	0	0	0	0	0	0	0	0	0	0	+	0	+	0	0	0	0	0	0	0
Palpable spleen	+	+	—	+	0	—	+	0	—	0	0	0	+	0	0	0	0	+	0	0
Enlarged heart	+	—	—	—	0	+	—	—	—	+	+	0	+	+	+	+	+	+	+	+
Murmurs of aortic insufficiency	+	+	+	+	+	+	+	+	?	+	+	0	?	+	+	+	+	+	+	+
Varying intensities of murmurs	0	0	0	+	0	0	+	0	0	0	0	0	0	0	0	0	0	0	0	0
Pulse pressure in mm. Hg.	—	80	—	—	85	140	—	122	43	141	134	55	60	120	110	110	80	75	180	100
Corrigan pulse	—	+	—	—	—	+	—	—	—	+	+	0	+	+	+	+	+	+	+	+
Anemia	+	+	—	+	+	—	+	+	+	0	+	+	+	0	+	0	+	+	+	+
Leukocytosis	—	+	—	0	+	—	+	+	0	0	+	+	0	0	0	0	+	+	+	0
Hematuria	—	+	—	0	+	—	+	+	0	0	0	0	0	0	+	0	0	+	0	0
Duration of endocarditis in months	12	—	—	8	1	—	10	—	½	1 (?)	1	½	6	—	2½	12	3	6	10	½ (?)
Diagnosis ante mortem	+	+	0	0	0	0	+	0	0	0	0	0	0	0	0	0	0	+	0	0

* The dashes indicate lack of information.

† The patients having antisyphilitic therapy were inadequately treated. Where Wassermann reactions of the blood were stated as being negative there were histories of treatment.

‡ Abbreviations regarding temperature indicate intermittent, septic, continuous and remittent.

TABLE 4.—*Tabulation of Essential Pathologic Data of 20 Cases of Bacterial Endocarditis Superimposed on Syphilitic Aortic Valvulitis*

	Case																		
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
Syphilitic aortitis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Syphilitic valvulitis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Aortic insufficiency	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiac hypertrophy	+	+	+	+	+	+	+	+	—	+	+	0	+	+	+	+	+	+	+	+
Other evidences of syphilis	—	—	—	—	+	—	—	+	—	0	—	0	+	0	0	0	0	0	0	0
Previous valvular changes other than syphilitic	0	0	—	0	0	0	—	0	0	0	0	0	0	0	0	0	0	0	0	0
Type of endocarditis†	S	A	S	S	A	S	S	A	A	S	A	A	S	S	S	S	S	S	S	A
Mycotic aneurysm	0	+	0	0	0	+	—	0	+	+	+	+	0	+	0	+	0	+	+	0
Myocarditis	—	—	—	—	—	—	+	0	—	0	0	0	0	0	+	+	0	0	+	0
Pericarditis	—	—	—	—	—	—	—	—	—	0	+	0	0	0	0	0	0	0	0	0
Infarcts: Spleen	—	—	0	—	+	0	—	+	+	0	0	0	0	0	0	0	+	+	0	+
Infarcts: Kidney	—	—	+	—	+	0	—	0	0	0	0	+	0	0	+	0	0	0	+	0
Infarcts: Brain	—	—	0	—	0	0	—	0	0	0	0	0	0	0	0	0	+	+	0	0
Nephritis	—	+	—	—	—	0	—	+	—	0	0	0	+	0	+	0	+	0	+	0
Acute splenic tumor	—	—	+	+	—	0	—	+	—	0	+	+	+	0	0	+	0	+	0	0

* For a description including the location of the vegetations see the analysis of pathologic data in the text. The dashes indicate lack of information.

† Abbreviations indicate the type of endocarditis as subacute or acute.

Laboratory Data.—The urine was clear and amber colored, and the specific gravity was 1.028. It had an acid reaction and contained albumin (1 plus) but no sugar; occasional white cells and granular casts were seen. The Fishberg concentration test (unsatisfactory) showed a fixed specific gravity at 1.015. The phenolsulfonphthalein test showed 60 per cent excretion. Examination of the blood revealed 3,400,000 red cells and 12,000 white cells. The hemoglobin content was 60 per cent and the differential smear normal. Blood cultures were not made. The Wassermann reaction of the blood was positive. The Wassermann reaction of the cerebrospinal fluid was positive. The colloidal mastic curve was 3321000000. The chemistry of the blood was normal. A roentgenogram of the chest confirmed the cardiac enlargement and the congestive changes in the lungs. There was some fluid at the base of the right lung.

Clinical Course.—The patient improved during the first month on being given digitalis and diuretics and being treated with general therapeutic measures. He did, however, show fluctuations of temperature of an intermittent character, the elevation never going above 101.2 F. (38.4 C.). On Dec. 21, 1937, he was transferred to the wards for patients with chronic conditions. At this time there were noted systolic and diastolic murmurs over the aortic region, as well as an apical systolic murmur. The patient was relatively free from edema. About six days after transfer, the temperature having been 98.4 F. (36.9 C.) for three days, an infection of the upper respiratory tract developed, with a mild pharyngitis, and his temperature rose to 100 F. (37.8 C.). Edema of the face became apparent, but there were no significant urinary changes. Generalized edema again made its appearance, and his condition gradually became more critical. For the last few days of life he was restless, dyspneic and uncooperative, and he had some blood-tinged sputum. There were never any petechiae. He died on Feb. 1, 1938, slightly more than three and one-half months after the onset of his symptoms. For the last two weeks of life his temperature was normal. Bacterial endocarditis was not suspected.

Autopsy.—Anatomic Diagnosis: Examination revealed syphilitic aortitis, syphilitic valvulitis and aortic insufficiency; left ventricular hypertrophy and dilatation were present, with mural thrombi in the right auricle and generalized chronic passive congestion. There was subacute bacterial endocarditis of the aortic valve, with gram-positive cocci, possibly Str. viridans, and there was a small mycotic aneurysm in the right sinus of Valsalva, with a ruptured mycotic aneurysm of the right aortic cusp; healing vegetations on the aortic valve were present and an infarct in the spleen. Examination revealed an old area of encephalomalacia in the right occipital lobe, and there was scarring in the thyroid gland.

Gross Description of the Heart and Aorta: The heart was markedly hypertrophied and dilated, especially the left ventricle, and it weighed 720 Gm. There were small mural thrombi in the right auricle but nowhere else. At the root of the aorta there was typical syphilitic aortitis, with marked wrinkling and puckering of the intima and thickening of the adventitia. The breaks in the media were readily visible. This syphilitic process was directly continuous with a similar process in the sinuses of Valsalva, and from there it passed down to the aortic cusps. The aortic ring was slightly dilated. The commissures between the left and the middle cusp were thickened and fused for a distance of about 1 cm. from their attachments. The left cusp had its margin displaced 6 mm. below the level of the others. There was a slight fusion of the right and the middle cusps. The valve, then, was obviously insufficient. The occlusal edges of the cusps were thickened and rolled. On the ventricular surfaces of the right and middle cusps there were

small yellow and white granular vegetations. This process was most extensive on the right cusp. The vegetations were in part friable, but there were also older, tough areas which were definitely organized. Some of the vegetations extended down on the endocardium of the membranous septum, but none were present along the free margins of the valve cusps. There was a small bulge at the base of the right cusp, and here there was a perforation guarded by several small vegetations.

In the sinus of Valsalva, behind the small bulge, there was a little irregular opening in the endocardium, and a small aneurysm, 5 mm. deep, was found. The base of this could be seen as a yellow opaque spot in the musculature of the pulmonary conus behind the tricuspid valve. The middle cusp contained a small gray vegetation on a portion of the corpus arantii. It measured 5 mm. across and was tough. The mitral valve was delicate, and its chordae tendineae showed nothing. The pulmonary and tricuspid valves were normal. The coronary arteries were delicate. In the aorta the syphilitic process extended from the sinuses of Valsalva into the ascending portion and arch. The very first part of the innominate artery was also involved by the process. The wrinkling ended at a point just beyond the subclavian artery on the left. The remainder of the aorta showed only slight changes which consisted of a few fatty streaks in the intima.

Microscopic Lesions of the Heart: The myocardium in the immediate vicinity of the aortic valve contained a small number of dense fibrous scars with a few lymphocytes about them. There was scarcely any scarring in the remaining muscle. In the right auricular appendage there were a few very slightly organized small thrombi. The mitral valve and its elastic tissue were normal. A small artery and a portion of the left circumflex artery in the sections showed no changes. There were no evidences of previous rheumatic changes.

Microscopic Lesions of the Aorta, the Aortic Valve and the Sinus of Valsalva: Several sections from different portions of the aorta all showed an advanced syphilitic process. The adventitia was thickened by dense, wavy fibrous tissue which was partly hyalinized. Many vasa vasorum and small arteries contained large collars of lymphocytes and plasma cells. Moderate numbers showed various stages of obliterative endocarditis. The media was markedly altered. There were many young stellate vascular scars with numerous lymphocytes and plasma cells about them. Numerous other dense fibrous scars caused a thinning out and many interruptions of the elastic tissue. No fresh necroses were present. The intima was irregularly thickened, was somewhat granular and showed the early changes of arteriosclerosis. It was only a little scarred. In the right sinus of Valsalva the syphilitic process was even more accentuated. There were numerous large adventitial collections of lymphocytes and plasma cells about many blood-containing capillaries and stellate scars. In the media the elastic tissue stopped abruptly at the base of the aortic valve. Here it was replaced by a dense, whorled, disordered hyaline mass in which small capillaries and focal collections of lymphocytes were embedded. The proximal portion of the valve was thickened by fibrous connective tissue in which there were numerous fibroblasts, lymphocytes and polymorphonuclear leukocytes. A little farther out the valve became hyaline and was completely perforated. From this point on, a second process of a bacterial nature was superimposed on the syphilitic lesion. The valve was distorted and heavily scarred. There were many capillaries containing red corpuscles, and the polymorphonuclear leukocytes were very numerous. At one point in the middle of the cusp the leukocytic infiltration was extremely intense, and many of the cells appeared disintegrated. Here the valve was thinner than elsewhere and somewhat necrotic, and one might suppose that this could have been the site of another

perforation. Here too there were many small capillaries, almost to the point of hypercapillarization. In one area the inflammatory vasculature in the valve consisted of large anastomosing and often stellate blood-containing channels, referred to by Gross and Fried [5] in their cases of subacute bacterial endocarditis as the "spongy lesion." Beyond this point the process suddenly stopped, and the occlusal part of the cusp showed only dense fibrous tissue and was club shaped. The surface of the valve in this portion contained only a small amount of hyaline material and no bacteria. The endothelium of the entire valve was irregularly thickened by proliferating and inflammatory cells. Attached to the endocardium of the sinus of Valsalva was a thin mass of fibrin and gram-positive cocci. This vegetation lined the edges of the perforation previously mentioned and passed through it to the ventricular surface of the cusp. Here the masses of bacteria were large and appeared as dense clouds. Many old and previously dead cocci had lost their gram-positive staining characteristics and were now gram-negative. Some of the vegetations were partially organized and capillarized. At their bases they contained thin spindle-shaped fibroblasts and large oval and polygonal and mononuclear cells, with deeply staining nuclei and basophilic cytoplasms. Some of the latter cells were multinucleated. They were most frequently found at the bases of the organized vegetations and were reminiscent of endothelial cells or macrophages. The presence of these cells, when coupled with the organization of the vegetations and the large number of capillaries, bespeaks a subacute rather than an acute inflammatory process. Some of the fibrinous masses which were only slightly organized contained polymorphonuclear leukocytes in small clumps, and some of these in turn were necrobiotic. In no instance were there heavy polymorphonuclear leukocytic infiltrations at the bases of the vegetations. At most there were small numbers of lymphocytes and leukocytes, the former predominating.

TABLE 5.—*Age Incidence*

	Decades						
	I	II	III	IV	V	VI	VII
Acute.....	0	0	21 (28.6%)	3 (42.9%)	1 (14.2%)	1 (14.2%)	7 (35%)
Subacute....	0	1 (7.7%)	4 (30.1%)	4 (30.1%)	3 (23.1%)	1 (7.7%)	13 (65%)
Totals....	0	1 (5%)	6 (30%)	7 (35%)	4 (20%)	2 (10%)	20 (100%)

ANALYSIS OF CLINICAL DATA

The following analysis is based on the 11 cases collected from the literature as well as on our own 9 cases. The cases will be referred to by their numbers in tables 3 and 4, our cases being 12 to 20 inclusive. The age incidence is shown in table 5.

From table 5 one can see that acute and subacute endocarditis occurred most frequently in early or middle adult life. In the cases of the acute type the patients' ages varied from 35 years to 63 years. In the cases of the subacute type the age variance was from 23 to 61 years. These figures parallel those usually given for acute and subacute bacterial endocarditis, but they are too small to permit generalization. The average age was higher in white than in colored patients.

With both acute and subacute endocarditis the incidence was much greater in men than in women (table 6). The ratio tallies with that of uncomplicated syphilitic aortitis, but it is in contrast to the usually stated lower ratio between the sexes in the usual cases of bacterial endocarditis (i. e., 1½:1 or 2:1).

Nine, or 45 per cent, of the patients were white; 10, or 50 per cent, were colored. In 1 case no mention of race was made. In the cases in the literature the patients were predominantly white, while in 8 of our 9 cases the patients were colored. In 1,000 consecutive routine autopsies at this hospital, 595, or 59.5 per cent, of the patients were colored and 405, or 40.5 per cent, were white. In most of the cases the patients were colored.

Type and Duration of Endocarditis.—In 7 cases (35 per cent) the disease was acute and of less than one month's duration. In 13 (65 per cent) the disease was subacute. In the latter cases the shortest duration was two and a half months and the longest twelve months (table 3).

TABLE 6.—*Distribution as to Sex*

	Men	Women	Totals
Acute	6 (85.7%)	1 (14.2%)	7 (35%)
Subacute	12 (92.3%)	1 (7.6%)	13 (65%)
Totals	18 (90%)	2 (10%)	20 (100%)

Serologic Examinations.—The Wassermann reactions of the blood were positive in 17 cases (85 per cent). In 3 (15 per cent) the reactions were negative, but histories of antisyphilitic therapy were obtained. It is of interest to note here that several authors [20] have commented on the occurrence of false positive Wassermann reactions of the blood in the course of subacute bacterial endocarditis. The Wassermann reactions of the spinal fluid were positive in 5 cases, negative in 8 and not recorded in 7.

Duration of Syphilis.—The duration of syphilis was known in only 10 cases. The shortest was four years (23 year old Negro man), and the longest was forty-six years (63 year old white man).

Antisyphilitic Therapy.—In 8 cases (40 per cent) the patient received inadequate therapy; in 9 cases (45 per cent) the patient received none, and in 3 no mention was made concerning this point.

History of Rheumatic Fever.—In 18 cases (85 per cent) the patients stated they had never had rheumatic fever, and in 2 cases this information was not recorded.

20. Landau, A., and Held, J.: Sur la réaction de Bordet-Wassermann positive au cours de l'endocardite lente, Bull. et mém. Soc. méd. d. hôp. de Paris **49**:1322 (Oct. 16) 1925. Kaldewey, W.: Ueber den Wert der Wassermann Reaktion bei Endocarditis, Deutsche med. Wchnschr. **49**:443 (April 6) 1923.

Portal of Infection.—Of the 7 cases of acute endocarditis the portal or method of entry was known in 3 cases. It appeared to be: (1) intravenous administration by the "morphine addict" of unsterile tap water (case 8), (2) prostatic abscess (case 9) and (3) pneumococcic lobar pneumonia with septicemia (case 12). Of the 13 cases of subacute endocarditis the portal of entry was unknown in every case, and the postmortem observations were not illuminating on this point.

Manner of Onset.—In the cases of the acute type symptoms of severe septicemia predominated. There was also extreme dyspnea in 4 of the 7 cases. In the cases of the subacute type the onset was similar to that in the usual cases of subacute bacterial endocarditis. In most of the cases, however, severe dyspnea appeared early and was followed on the average of two to three months later by peripheral edema and orthopnea. Therapy for cardiac failure was of no avail. Conspicuous by their absence were chills, chilly sensations and subjective sense of fever.

Type of Fever.—In the cases of acute endocarditis the temperatures were more septic. In the cases of subacute endocarditis the elevations were slight and intermittent, with morning fall, evening rise and slight variations in the daily peaks. Normal temperatures were present in 3 (23 per cent) of these cases.

Petechiae.—Only 1 patient with acute endocarditis had petechiae. Among those with subacute endocarditis 5 (38.6 per cent) had petechiae. This is definitely less than is found in the usual cases of subacute bacterial endocarditis.

Embolic Phenomena.—Only 1 patient with acute endocarditis had Osler nodes. In those with subacute endocarditis 6 (46.1 per cent) complained of tenderness over the splenic area and of Osler nodes. In 2 of these patients evidence of cerebral embolism was present (cases 7 and 18).

Palpability of the Spleen.—In 1 patient with acute endocarditis and in 5 (38 per cent) with subacute endocarditis the spleen was palpable.

Clubbed Fingers.—One patient with acute endocarditis and 1 with subacute endocarditis (congenital) had hippocratic fingers.

Arthritis.—In no case was there arthritis.

Occurrence of Nephritis.—Three of the patients with acute endocarditis and 2 with subacute endocarditis had clinical nephritis. This represents 25 per cent of all the cases and is distinctly a lower incidence than is usually found in endocarditis.

Character of Pulse.—Twelve patients (50 per cent) had a collapsing (Corrigan) pulse, and in 8 cases no mention was made of this condition.

Blood Pressure.—Fifteen patients (75 per cent) had blood pressures typical of aortic insufficiency. Average pressures were: systolic, 148 mm. of mercury, and diastolic, 44 mm. of mercury; the pulse pressure was 85 mm. of mercury.

Cardiac Physical Findings.—Twelve patients (60 per cent) showed predominantly left ventricular enlargement; 2 patients had small enlargements, and regarding 6 patients no mention was made of ventricular enlargement. Four patients had diastolic thrills. Seventeen (85 per cent) had to and fro murmurs which were not altered at any time during the course of the disease.

Roentgenographic Findings in the Heart.—The left ventricle was enlarged in 10 (50 per cent) of the cases and normal in 3. No mention of roentgenographic findings was made in 7.

Urinary Findings.—Red blood corpuscles were found in the urine of 6 (30 per cent) of all the patients. In 11 cases no blood was present, and in 3 this point was not mentioned. Albumin was found in 10 (50 per cent) of the cases.

Blood Findings.—In all the cases in which the condition was acute the anemia was severe, the red blood corpuscles numbering less than 2,500,000 in 5 of the 7 cases. Polymorphonuclear leukocytosis was well pronounced in all. Of the patients in whom the condition was subacute 8 had red blood corpuscle counts of less than 4,000,000. The leukocyte counts were not excessive. Hemoglobin values varied from 42 to 88 per cent and were proportional to the red blood corpuscle counts.

Course and Termination.—In the cases of acute endocarditis the symptoms of septicemia became progressively worse, with death occurring within four weeks. The aortic insufficiency did not appear to be influenced in any way by the superimposed bacterial endocarditis. The correct diagnosis was made in 1 case.

The course of the cases of subacute endocarditis was similar to that seen in usual subacute bacterial endocarditis except that cardiac failure was more prominent than is ordinarily observed. This condition was present in 11 (84.6 per cent) of the 13 cases of subacute endocarditis and greatly overshadowed the much subdued bacterial endocarditis. The correct diagnosis was made in 3 of the 13 cases.

Summary of Main Clinical Characteristics of Bacterial Endocarditis Associated with Syphilitic Aortic Valvular Insufficiency.—The foregoing analysis of the clinical data showed that bacterial endocarditis may be engrafted on the aortic valves in cases of syphilitic aortic valvular insufficiency as two distinct types, acute bacterial endocarditis and subacute bacterial endocarditis. These types of endocarditis were found to be similar in most respects to those usually encountered in cases of acute

and subacute bacterial endocarditis. They do, however, present certain differences which we shall here summarize:

1. Acute endocarditis. There was a marked prevalence of this form of endocarditis in men, and there was positive evidence of syphilis in all cases, with absence of a history of rheumatic fever; marked dyspnea occurred at the onset of the disease, as well as typical physical changes referable to cardiovascular syphilis; roentgenographic evidence indicated that the aorta was widened and the heart enlarged to the left; there was no alteration of preexistent murmurs.

2. Subacute endocarditis. There was a marked prevalence in men and positive evidence of syphilis, with absence of a history of rheumatic fever in all the cases; absence of chills, chilly sensations or subjective sense of fever was typical in practically all the cases (91 per cent), progressive dyspnea was prominent early in the disease, with peripheral edema setting in about two to three months later. The incidence of petechiae (38.6 per cent) was diminished, in contrast to the usual 60 to 70 per cent, with diminution in the incidence of embolic phenomena (38.6 per cent), in contrast to the usual 85 to 90 per cent; there was absence of cerebral embolism in all but 2 cases, with reduction in the incidence of nephritis (15.3 per cent) in contrast to the usual 40 to 50 per cent; the color of the skin was not said to be altered in any of the cases; typical physical changes were referable to cardiovascular syphilis and the constancy of existing murmurs; roentgenographic evidence indicated that the aorta was widened and the heart enlarged to the left; the course was typically one of syphilitic cardiovascular involvement with signs of myocardial failure (left ventricular) predominating and the bacterial process very much subdued; the correct diagnosis was made in 3 (23 per cent) of these cases.

BACTERIOLOGIC STUDIES

We shall include here the results of studies done intra vitam and post mortem.

Acute Endocarditis.—Blood cultures (intra vitam) were made in 6 of the 7 cases. In cases 5 and 11, 2 cultures were made for each patient, but no growths were observed. From the blood obtained in case 2 a nonhemolytic streptococcus was grown on three separate occasions. In case 9, a blood culture made about two weeks before death showed a growth of Staphylococcus albus (urine cultures also yielding Staph. albus). In case 12 material for a blood culture taken twelve days before death yielded a pure growth of pneumococci (untyped), and eleven days later (a day before death) the spinal fluid culture also contained pneumococci. In case 8, although blood for a culture was not taken intra vitam, a postmortem culture of material

taken from the spleen showed a pure growth of hemolytic Staph. aureus. In only 1 other case was material taken for a postmortem culture (case 9). This culture showed the same organisms as were present during life (Staph. albus). In case 20 no cultures were made.

In all the cases the organisms were stained as gram-positive in the bacterial vegetations themselves. In case 12 the bacteria were lancet-shaped diplococci for the greater part. In case 8 they were grouped as clumps of cocci, while in the other cases no note as to the morphology of the bacteria was made. No cultures were made in case 20.

Table 7 shows the organisms found intra vitam and post mortem.

Subacute Endocarditis.—In contrast to the cases in which the disease was acute and in which septicemia was obvious, blood cultures (intra vitam) were not made in most of the cases in which the disease was subacute. As has already been pointed out, the reason for this was that in most of the cases the correct diagnosis was not suspected during life.

TABLE 7.—*Bacteriologic Studies in Acute Cases*

Organisms	Number of Cultures	Material
Nonhemolytic streptococcus (case 2)	3	Blood (intra vitam)
Hemolytic Staph. aureus (case 8)	1	Spleen (post mortem)
Staph. albus (case 9)	2	Blood (intra vitam, 2 weeks before death and post mortem)
Pneumococcus (case 12)	1	Blood (intra vitam, 12 weeks before death)
No growth (cases 5, 11)	2 each	Blood (intra vitam)
No culture (case 20)		

In 9 cases (4, 6, 10, 14, 15, 16, 17, 18 and 19) no cultures were made intra vitam. In 2 others, the cultures showed no growths repeatedly (case 1, negative results twice, and case 13, negative results three times). In 1 instance (case 3) a blood culture showed a growth of Str. viridans. In 1 case (case 7) 2 cultures showed growths of "strepto-enterococcus" (also called Str. viridans [78]).

Postmortem cultures were made in 3 cases and were not made in 10. Of the 3 cases in which cultures were made, in 2 (cases 6 and 10) they showed growths of Str. viridans, and in 1 (case 18) there was a nonhemolytic streptococcus. In case 10 there were intestinal infarcts as well as generalized peritonitis, and it was stated by the authors that Str. viridans was recovered in pure growth from the peritoneal cavity. The blood cultures also showed a growth of this organism.

It appears, then, that in the cases in which cultures were made (intra vitam and post mortem) Str. viridans was found in 4 cases (3, 6, 7 and 10), a nonhemolytic streptococcus in 1 (case 18), and no organisms were found in 2 cases (1 and 13). Table 8 summarizes the bacterial organisms observed in the cases of subacute endocarditis.

Bacteria were stained in the valvular vegetations in all the cases. The morphology of the organisms was not, however, always mentioned. In our own cases the organisms appeared as gram-positive cocci. Occasionally, chains or diploformations were noted, but most often the organisms were arranged in clumps. Frequently the cocci also stained gram-negative. This would indicate, according to the technic used,[19] that numbers of the organisms which were nonviable intra vitam presented altered staining reactions post mortem. This change was noted in 6 of our 7 cases of subacute endocarditis (cases 13, 14, 16, 17, 18 and 19). The type of valvular reaction seen in all our cases of the subacute type was very reminiscent of the usual changes seen in endocarditis due to Streptococcus viridans, except that there was even greater tendency toward healing.

TABLE 8.—*Bacteriologic Studies in Subacute Endocarditis*

Organisms	Number of Cultures	Material
Str. viridans (case 3)	1	Blood (intra vitam)
Str. viridans (case 6)	1	Blood and valve (post mortem)
Streptoenterococcus (case 7) (Str. viridans)	2	Blood (intra vitam)
Str. viridans (case 10)	1	Blood and peritoneal cavity (post mortem)
Nonhemolytic streptococcus (case 18)	1	Blood and valve (post mortem)
No growth in 2 cases (1 and 13)	2 and 3, respectively	Blood (intra vitam)
No cultures in 6 cases		

ANALYSIS OF PATHOLOGIC DATA

For the sake of convenience the syphilitic and the bacterial changes will be separated; however, in all the cases both processes existed on the same valves. The gross and microscopic alterations will be considered together and not described in detail, since these changes have been mentioned extensively by other authors.[21]

Syphilitic Changes.—Aortitis: In all the cases evidence of syphilitic aortitis was present. In 4 cases the exact distribution of the aortitis was not mentioned. The ascending aorta was involved in 16 cases, and the sinuses of Valsalva were implicated in all these cases. In 5 cases the arch of the aorta was involved. In 4 cases the entire aorta was affected. In 2 cases there were syphilitic aneurysms, in the sinus of Valsalva (case 5) and in the ascending aorta (case 6). In no instance were vegetations implanted on the aorta itself.

There did not appear to be any correlation between the degree or the extent of the aortitis and the size or extent of the bacterial vegetations.

Valvulitis: Evidence of valvulitis was present in all the cases. In case 16, the syphilitic process was stated as extending into the sinuses of Valsalva. The commissures were widened, and where there were no

21. MacCallum.[1a] Gross and Fried.[5]

vegetations the thick, cordlike occlusal margins and retraction of the cusps were apparent.

Aortic Valvular Insufficiency: All the valves were described as being insufficient. We realize that bacterial endocarditis itself could have accounted for some of the valvular insufficiency. In an attempt to correlate the sizes of the bacterial vegetations with the degree of insufficiency it was noted that in most of the cases in which the cardiac weights were mentioned the sizes of the bacterial vegetations were inversely proportional to the sizes of the hearts. This would be another point in favor of preexisting valvular insufficiency, since usually in the absence of other causes one finds large vegetations destroying the valve leaflets in the cases of endocarditis associated with valvular insufficiency.

Cardiac Hypertrophy: The heart was enlarged in 18 cases. The average weight was 645 Gm. A comparison of these cardiac weights with those found in our cases of subacute endocarditis superimposed on rheumatic aortic valves revealed that in the latter there was less hypertrophy, the average weight being 500 Gm. This, we feel, represents a significant difference.

Other Evidence of Syphilis: Other syphilitic anatomic changes were evident in 3 cases: tabes dorsalis (case 5), possible meningitis (case 8) and orchitis (case 13).

Changes Due to Bacterial Endocarditis.—Type of Endocarditis: In 7 cases (35 per cent) the disease was acute, and in 13 cases (65 per cent) it was subacute.

Location of Vegetations: In all the cases the primary vegetations were located on the aortic valve cusps. There was no essential difference between the locations of the vegetations in the cases of both acute and subacute endocarditis; hence they are considered together.

In 5 cases all the aortic cusps were involved (4 of these being of the subacute type). The individual cusps were affected in the following manner: left cusp, 8 cases; right cusp, 8 cases; and the cusp not associated with a coronary orifice, 11 cases. The sinuses of Valsalva were involved in 3 cases and the left ventricular surface of the membranous septum in 4.

One other observation is noteworthy. In 8 of our own 9 cases, the vegetations were not on the occlusal margins of the valve cusps but rather on the ventricular surfaces and bases of the leaflets (figs. 1 and 5). There was no tendency for the vegetations to grow around the margins of the cusps and thus involve both sides. These features are distinctly in contrast to those in the usual form of subacute bacterial endocarditis, in which the vegetations (even rheumatic verrucae) are practically always found along the occlusal margins of the valve leaflets on both sides. The significance of these facts will be considered when the pathogenesis is discussed. In the cases taken from the literature no

mention concerning these points was found. Contact vegetations were present on the aortic surface of the anterior mitral leaflet in 8 cases; on the chordae tendineae in 4 cases and in the left auricle in 2 cases. In none of the cases were any of the vegetations implanted on the syphilitic process in the aorta.

Description of Vegetations: In 3 of the cases of acute endocarditis the vegetations were described as being large or bulky, friable, wartlike

Fig. 1.—Heart in case 15, with syphilitic aortitis, valvulitis and large vegetations at bases and over ventricular surfaces of posterior and left aortic cusps. The thickened chordae tendineae show small stringy vegetations.

or sessile and gray or dark red. In the 3 remaining cases of acute endocarditis they were stated as being small, granular or flat, friable, yellow or yellow-gray and necrotic. Only 3 microscopic notes were recorded in the cases of this type, and these agreed completely with the usual descriptions of acute endocarditis.

In 10 cases of subacute endocarditis (77 per cent) the vegetations were small instead of being predominantly large, bulky and irregular,

as are the vegetations in most of the usual cases of subacute endocarditis. In only 2 cases (7 and 15) were there large "voluminous or polypoid" vegetations. The sizes of the others varied from "thin, granular layers" to layers 5 or 6 mm. in diameter. In 7 cases the vegetations were described as being numerous, and in 6 they were localized to only one of the aortic cusps. The amount of organization did not always receive

Fig. 2.—Photomicrograph of a section of aorta in case 15, showing numerous stellate and vascular medial scars with scattered inflammatory cells. In the lower part of the photograph a tiny vessel is completely obliterated and partially surrounded by a cuff of lymphocytes and plasma cells. A larger, adjacent artery is almost completely occluded by an obliterative endarteritis. Hematoxylin and eosin stain; × 46.

comment. In 7 of our 9 cases of the subacute type the bases of the vegetations were said to be tough and organized, while their surfaces were fairly friable. In 4 of the other cases the vegetations were stated as being partly organized or else just "friable." The colors of the

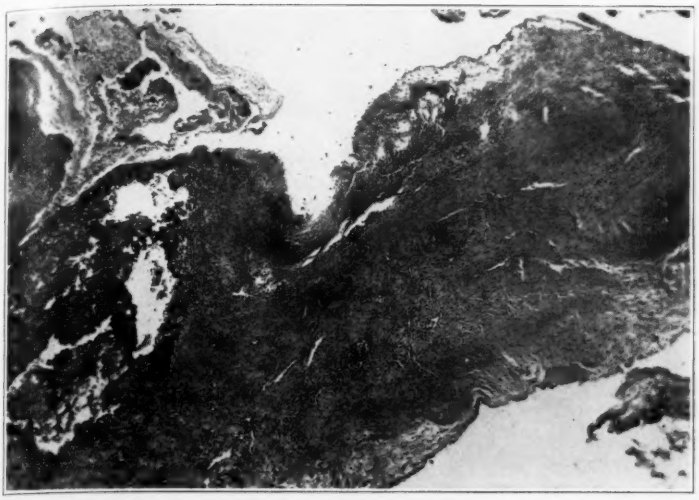

Fig. 3.—Photomicrograph of a section through the base of an aortic cusp showing vegetation in case 15. On the right side of the photograph the valve is scarred by dense hyaline tissue. In the body of the valve there are very numerous small blood channels, as well as large numbers of inflammatory cells. The left side of the photograph shows a portion of the bacterial vegetation with destruction of the subjacent part of the valve. Hematoxylin and eosin stain; × 91.

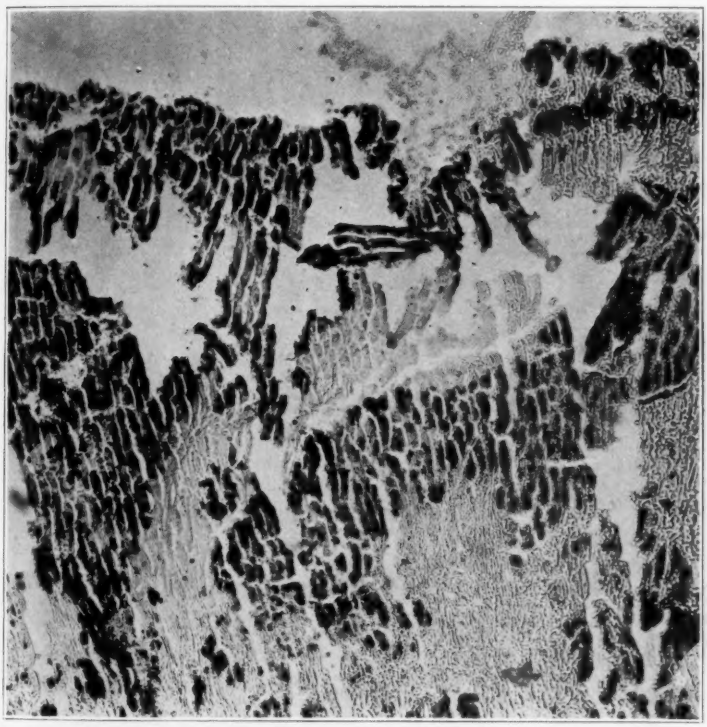

Fig. 4.—Photomicrograph of bacterial vegetations in case 15. The numerous black areas represent solid clumps of gram-positive cocci. Brown and Brenn bacterial stain; × 46.

vegetations varied from pink, yellow, gray, and white to brownish yellow. In our own cases the aortic valve cusps were never stated as being extensively destroyed or distorted. The lack of these changes is again in contrast to the majority of the usual cases of endocarditis, in which such alterations are quite frequently described.

Microscopically, the condition in our cases was typical of the type of endocarditis seen in infections caused by Str. viridans, with the exception that in most instances there was distinctly more organization of the bases than is usually seen, and in the depths of the vegetations nonviable organisms were relatively more frequent. Microscopic descriptions were vague and lacking in most of the cases abstracted from the literature.

Mycotic Aneurysms in Valve Leaflets: Among the cases of the acute type there were 4 aneurysms: 2 in the right aortic cusp and 1 in each of the other two cusps. There was also 1 aneurysm each in the anterior mitral leaflet and the right sinus of Valsalva. Two of the aneurysms were ruptured.

Among the cases of the subacute type there were 6 mycotic aneurysms affecting the aortic cusps: 2 in the right aortic cusp and 2 in each of the other 2 cusps. The anterior and posterior mitral leaflets and membranous septum also showed 1 aneurysm each. Five of the aneurysms in this group were ruptured. In our cases the mycotic aortic valvular aneurysms were ruptured at the bases of the cusps.

Embolic aneurysms were not mentioned in any of the cases.

Myocarditis: Among the cases of the subacute type focal areas of acute myocarditis were noted in 3 cases (15, 16 and 19). In case 7 there were "Bracht-Wachter" lesions. In 9 cases there was no evidence of myocarditis, and in 7 no description was given. There was no evidence of rheumatism in any of the cases.

Pericarditis: In case 11 only was there subacute fibrinous pericarditis. This change was absent in all of our cases and not mentioned in the remaining cases.

Embolic Phenomena: In 5 of the cases of the acute type there were septic infarcts; in 4 cases the infarcts were splenic; in 1 the infarct was renal, and in 1 case both splenic and renal infarcts were present.

In the cases of the subacute type embolic phenomena were distinctly reduced in number. In 5 cases there were evidences of emboli. In cases 17 and 18 there were splenic infarcts and old areas of encephalomalacia; in cases 3, 15 and 19 there were renal infarcts. In case 10 there was an embolus in the superior mesenteric artery, and there was widespread infarction in the patient's bowel. In 4 other cases there were no evidences of embolic phenomena, and in 3 this point was not mentioned.

Nephritis: In the cases of acute endocarditis there were 2 cases in which the patients had glomerulonephritis; in case 2 the condition was

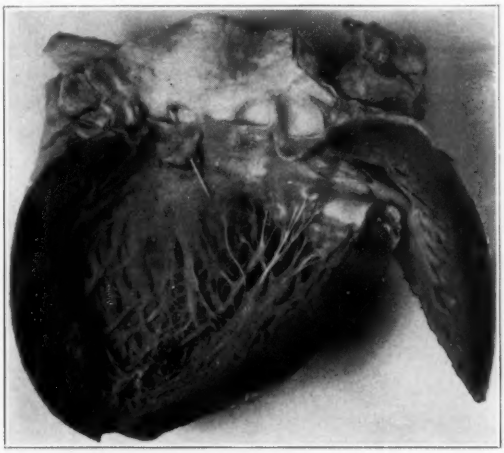

Fig. 5.—Heart in case 17, with syphilitic aortitis, and valvulitis with valves displaced at different levels (aortic insufficiency). Small bacterial vegetations are present on the ventricular surfaces of right and posterior cusps. Note probe passing through ruptured mycotic aneurysm at the base of right cusp.

Fig. 6.—Photomicrograph of a section through base of ruptured mycotic aneurysm and right aortic cusp in case 17. Note vegetative material lining edges of perforation, as well as heavy inflammatory reaction beneath vegetations. The more distal portion of the valve is heavily scarred. Hematoxylin and eosin stain; × 30.

acute and in case 8 it was subacute. In 3 cases nephritis was absent, and in 2 no mention was made concerning this point.

In the cases of subacute endocarditis there were only 4 patients who had subacute glomerulonephritis (cases 13, 15, 16 and 18). No bacteria or minute emboli could be found in the kidneys of our cases. Arteriolosclerotic nephritis was present in case 14. In 5 cases there was no nephritis, and in 3 this point was not mentioned. The incidence of

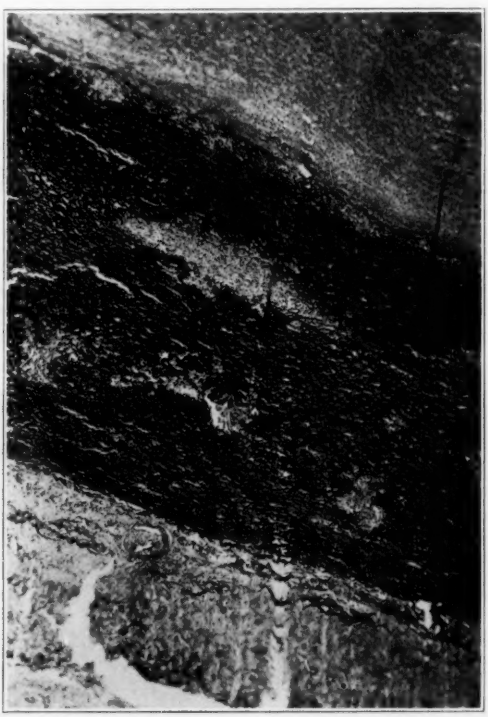

Fig. 7.—Photomicrograph of a section of aorta in case 17, showing syphilitic aortitis. White areas surrounded by the black represent medial interruptions and scars. The thick adventitia shows one small vessel with moderately advanced changes of an obliterative endarteritis. Verhoeff and Van Gieson elastic tissue stain; × 60.

nephritis at autopsy, then, was distinctly less than is found in the usual cases of subacute endocarditis.

Acute Splenic Tumor: In 3 cases of acute endocarditis (cases 8, 11 and 12) acute splenic tumors were noted, and in 1 case no such tumor was observed. In the other 3 cases no mention of this point was made.

In 5 cases of subacute endocarditis (cases 3, 4, 13, 16 and 18) acute splenic tumor was observed. In 6 cases none were observed, and in 2 cases no mention was made of this point.

Meningitis: Pneumococcic meningitis occurred in case 12, a case of acute endocarditis, and the exact type of organism was unknown.

Previous Valvular Changes Other Than Syphilitic: In 18 of the cases no other valvular lesions were present. In 2 cases there was no reference to this point.

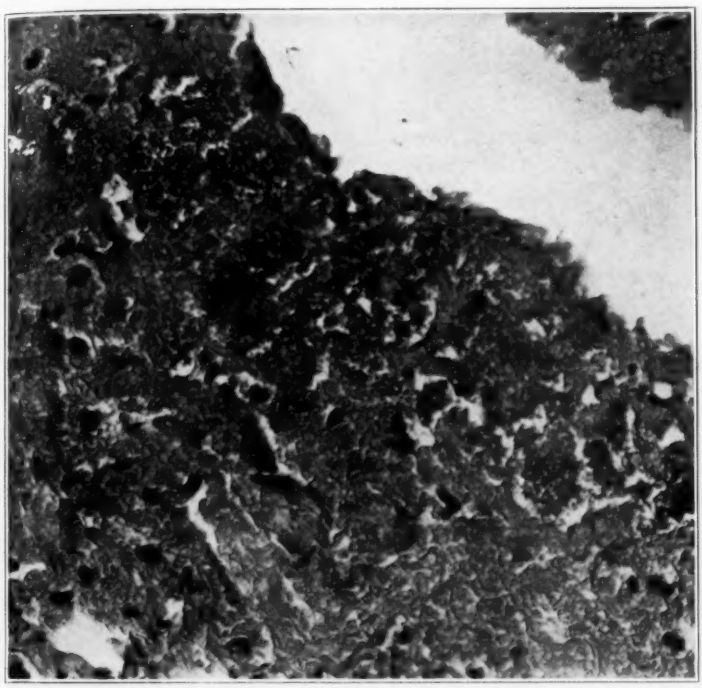

Fig. 8.—Photomicrograph of a section of right aortic cusp from case 6 showing vegetations containing gram-positive cocci in clumps, diplo formation and chains. The larger black areas represent nuclei of inflammatory cells. Brown and Brenn bacterial stain; × 1000.

Other Postmortem Observations: In 8 cases (40 per cent of the entire series), there was generalized chronic passive congestion, and in 2 cases anasarca was present. In 1 case there was pulmonary edema. In each of 2 cases (case 12, acute endocarditis, and case 7, subacute endocarditis), there were intimal abscesses in the aorta in the vicinity of the vegetations.

Summary of Main Pathologic Characteristics of Bacterial Vegetative Endocarditis Superimposed on Syphilitic Aortic Valvulitis.—At postmortem examination, two types of bacterial endocarditis were found superimposed on syphilitic aortic valvulitis, acute endocarditis and subacute endocarditis. In 4 of the cases of the subacute type cultures made either intra vitam or post mortem showed growths of Str. viridans. In none of the cases were there any lesions resembling those seen in association with rheumatic fever. These observations as well as those of other authors [22] are decidedly opposed to the old hypothesis that rheumatic valvulitis and subacute bacterial endocarditis due to Str. viridans are one and the same disease.[23] The majority of the observations made at autopsy were similar to those of the usual forms of bacterial endocarditis. The noteworthy differences are summarized below:

1. Syphilitic aortitis, valvulitis and aortic insufficiency were present in all of the cases. There was no evidence of rheumatism in any of the cases.
2. Cardiac hypertrophy was fairly pronounced in most of the cases, the average cardiac weight in this group being greater than in our rheumatic group, in which subacute bacterial endocarditis was superimposed on the aortic valves, on the mitral leaflets or on both.
3. Of the cases in which the exact locations of the aortic valvular vegetations were mentioned, the majority were exclusively confined to the ventricular surfaces and bases of the cusps with no tendency to involve either the occlusal margins or the opposite surfaces of the valve leaflets. In all of our cases rupture of mycotic aneurysms occurred at the bases of the cusps.
4. Distortion or destruction of the aortic valve cusps was not mentioned in any of the cases.
5. The sizes of the vegetations were just the reverse of what is found in the usual cases of bacterial endocarditis. In the cases of acute endocarditis most of the vegetations were described as being large. In the cases of subacute endocarditis the vegetations were small in the majority of instances. In our cases, also, the bases of these vegetations were more organized than usual and frequently contained gram-negative (nonviable) bacteria.
6. The incidence of embolic phenomena and nephritis was distinctly reduced in the cases of subacute endocarditis.

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22. (*a*) Koester, K.: Die embolische Endocarditis, Virchows Arch. f. path. Anat. **72**:257, 1878. (*b*) Grant, R. T.; Wood, J. E., Jr., and Jones, T. D.: Heart Valve Irregularities in Relation to Subacute Bacterial Endocarditis, Heart **14**: 247 (Aug.) 1928. (*c*) Nedzel, A.: Experimental Endocarditis, Arch. Path. **24**: 143 (Aug.) 1937. (*d*) Thayer.[8]

23. Sprague, H. B.: Subacute Bacterial Endocarditis, J. A. M. A. **94**:1037 (April 5) 1930. Levine.[6]

COMMENT

In the introductory remarks it was indicated that the occurrence of bacterial endocarditis engrafted on syphilitic aortic valves was regarded as rare. It was also intimated that one possible reason for this, in the more or less universal opinion of the investigators, was that the earlier recognition of rheumatic valvular disease and its association with bacterial endocarditis (especially the subacute variety) caused most observers to focus their attention almost exclusively on the relationship between these two pathologic entities. Consequently, many authors have stressed the point that previous rheumatic valvular lesions are prerequisite for the occurrence in most cases of bacterial endocarditis.[3] When one examines the analyses of a series of cases of endocarditis, however, frequently only the figures on the percentile occurrence on previously damaged rheumatic valves is given. These figures almost always vary from 60 to 80 per cent. What, then, is the basis for the occurrence of the disease in the remaining 20 to 40 per cent? Bicuspid normal and arteriosclerotic valves sometimes account for the remainder,[24] but most frequently no stated analyses are presented. Our own observations would indicate, moreover, that the combination of bacterial endocarditis and syphilitic aortic valvulitis is more common than is generally stated, and thus we are reasonably certain that further study of cases of endocarditis would reveal relatively more cases similar to the ones analyzed. This would be especially true of conditions occurring in regions where endocarditis and syphilis exist side by side. It is realized, however, that from the *absolute* point of view this combination of maladies is not nearly as common as the occurrence of bacterial endocarditis on valves previously altered by rheumatism; hence other explanations for this infrequency must be sought.

The pathogenesis of bacterial endocarditis has often been discussed.[22] Among the possible mechanisms that lead to the valvular implantation of bacteria, the hemodynamic factor of tension seems especially pertinent in this group of cases. It has already been pointed out [5] that the "formation of rheumatic verrucae in rheumatic cardiac disease is considerably influenced by mechanical stress and strain" and "the closure lines of those valve leaflets that are subjected to the greatest pressure changes (left ventricle) become the seat of verrucous formation." It has also been observed that in cases in which the valves "have become so stiffened that they cannot close, a new line of verrucae forms on the site most exposed to eddies and blood currents." More recently Nedzel [22c] has concluded from his experimental work that "pressor episodes" may play a role in the valvular preparation for bacterial implantation (adhesiveness), as well as in the causation of bacteremia. Furthermore, in a

24. Thayer.[3] Gross and Fried.[5]

variety of conditions [5] proliferative lesions (eosinophilic multinucleated inclusion bodies) are formed along the occlusal margins of the valves and may form a suitable site for anchorage of bacteria. These changes are stated to be more frequent on rheumatic valves than on normal ones. The mechanism for the formation of bacterial endocarditis on normal valves is the same as in the rheumatic. The components, however, are reduced in number, and herein lies at least a partial explanation for the reduced incidence of endocarditis on such valves.

Further evidence that the hemodynamic factors are intimately concerned in the causation and localization of bacterial vegetations is to be found in the examples of severe mitral stenosis. Such instances of "stiffened valves" have already been referred to, and superimposed bacterial endocarditis on valves so affected is extremely uncommon.[23] It might also be pointed out that in cases of chorea bacterial endocarditis is uncommon, while mitral stenosis is relatively frequent. Again, the incidence of rheumatic valvular disease in general and mitral stenosis in particular is greater in women, but the incidence of bacterial endocarditis is greater in men.[6] Among our own cases of rheumatism it has been found that in patients with advanced aortic insufficiency bacterial endocarditis was also very uncommon. Most of the cases of rheumatism with aortic bacterial endocarditis have been regarded by us as instances in which the altered valvular margins were still completely or partially capable of opposing each other. Moreover, the vegetations were primarily on the occlusal margins in these cases. It is also felt that if rheumatic aortic valvular insufficiency comparable to that associated with syphilitic valvulitis were present before the onset of bacterial endocarditis, cardiac hypertrophy should be greater in the former because of the added extensive destruction of the valve cusps. But, as a matter of fact, the average cardiac weights were less in the cases of rheumatism with bacterial endocarditis than in the cases of syphilis. The marked evidences of insufficiency observed in these cases, then, represent the effects of destruction of the valve cusps, in contrast to the almost uniform lack of such alterations in the cases of syphilitic aortic insufficiency.

When one comes to a consideration of the cases of syphilis, it becomes apparent that certain of the aforementioned predisposing factors suitable to the formation of endocarditis are absent. The valve cusps cannot approximate each other and consequently are unable to cause irritation of their scarred occlusal margins. Hence, they form a relatively poor anchoring ground for bacteria and vegetations. This, of course, is distinctly in contrast to what has been said about the rheumatic valves. The fact that in cases of syphilis the greatest tension and irritation are exerted on the ventricular surfaces and bases of the cusps explains most

satisfactorily the localization of the vegetations on the latter areas in most of our own cases. It would also account for the fact that the vegetations were small and showed marked tendency toward healing, because of less friction than is found between opposing lines of closure. In connection with these observations, it might be mentioned that bactericidal agents could conceivably be more efficacious than usual in the treatment of endocarditis in syphilitic patients, in view of the great natural tendency of the vegetations to heal.

The clinical and pathologic differences from the usual forms of subacute bacterial endocarditis have already been outlined. These departures from the usual forms of subacute endocarditis are explained by the alterations in pathologic findings as well. Thus, with the evidences of greater healing and smaller vegetations, the lessened incidence of petechiae, embolic phenomena and nephritis, as well as the very low grade sepsis can be explained. The lack of valvular destruction and the presence of small vegetations in most of the cases account for the constancy of the murmurs. The sepsis, though milder than usual, is enough to cause the moderate anemia and the general debility which the patients experience. The progressive cardiac failure with dyspnea and orthopnea is then to be expected in view of the extra load thrown on the already overburdened heart.

SUMMARY

The clinical and pathologic observations in 20 cases of bacterial endocarditis superimposed on syphilitic aortic valvulitis have been analyzed. Two types of endocarditis exist, acute and subacute. Both, though similar to the usual types of endocarditis, do present certain differences.

In cases of the acute type there was a marked prevalence in men in all the cases of this type there was positive evidence of syphilis and absence of a history of rheumatic fever; marked dyspnea was present at the onset of the illness, and there were typical signs of syphilitic aortic valvular insufficiency and septicemia. At autopsy the aortic valvular vegetations were described as large in most of the cases in which the size was mentioned. There were syphilitic aortitis, valvulitis, aortic insufficiency and cardiac hypertrophy in all. No changes due to rheumatic fever were present in any cases.

In the cases of the subacute type there was also a marked prevalence in men, and there was positive evidence of syphilis and absence of a history of rheumatic fever in all the cases in which this point was mentioned; no chills, chilly sensations or subjective sense of fever were reported in most of the cases; there was progressive dyspnea early in the disease, with peripheral edema setting in about two months later, reduced incidence of petechiae, embolic phenomena and nephritis; there

were no changes in the color of the skin of the white patients; typical syphilitic aortic valvular insufficiency was present, and the course was typically one of cardiovascular syphilis with signs of myocardial failure (left ventricular) predominating and endocarditis appearing subdued. Postmortem examinations revealed syphilitic aortitis, valvulitis and aortic insufficiency in all the cases; cardiac hypertrophy was pronounced, the average cardiac weight being greater than in the cases of rheumatism with aortic valvular bacterial endocarditis. In our cases the vegetations were noted on the *ventricular surfaces and bases* of the valves and not on the occlusal margins; the vegetations were small, with a marked tendency toward healing; destruction or distortion of the aortic cusps was not mentioned in any case; there was no evidence of rheumatic changes in any of the cases (i. e., in the valves and myocardium).

From the analysis of the bacteriologic studies it was found that in most of the cases acute endocarditis was caused by pyogenic organisms. In 1 case it was caused by a nonhemolytic streptococcus. In 2 cases materials taken for cultures repeatedly showed no growths, and in 1 case no cultures were made.

In the cases of subacute endocarditis Str. viridans was observed in materials taken for culture intra vitam in 2 cases and post mortem in 2 cases. A nonhemolytic streptococcus was observed in materials taken for culture post mortem in 1 case. In 2 cases cultures (intra vitam) repeatedly gave negative results, and in 6 instances no material was taken for culture.

The diagnosis of the simultaneous presence of both conditions is admittedly difficult, since not many clues are present to arouse suspicions of the existence of bacterial endocarditis. Aortic insufficiency will in most instances be readily perceived. Subacute endocarditis, however, will in most of the cases manifest itself only by a gradual progressive anemia, associated with slight daily intermittent rises in temperature, to 100 or 101 F. Without other explanation for these conditions (fever and anemia) bacterial endocarditis superimposed on syphilitic aortic valvulitis must be suspected, and blood cultures should be made repeatedly if negative results are given. (In practically all of our cases the temperature elevation was thought to be due to terminal pneumonia, while the anemia, in most instances, was ignored.)

When the evidences of subacute endocarditis are more outspoken (i. e., embolic phenomena, petechiae and nephritis), then the diagnosis becomes simpler, but it must be remembered that these frank forms of subacute bacterial endocarditis are only occasionally (as far as we could make out) implanted on syphilitic aortic valves. Most frequently they are located on rheumatic or normal valves, and the occurrence in these cases of positive Wassermann reactions would tend to throw one

off the right track. In the presence of definite syphilitic aortic insufficiency, bacterial endocarditis, if obvious, is most likely to be situated on a valve other than the aortic. This will probably be true in most cases, even though it may be known that syphilitic aortic insufficiency has existed for a long time before the present illness.

SUMMARY AND CONCLUSIONS

The clinicopathologic observations of bacterial endocarditis (acute and subacute) superimposed on syphilitic aortic valvulitis are presented in detail.

To the 11 cases found in the literature, 9 of our own have been added, the total of 20 "proved" cases including 7 of acute and 13 of subacute endocarditis.

That the diagnosis may be concomitant existence of the two conditions may be suspected when in the presence of syphilitic aortic valvular insufficiency a gradually progressive anemia exists with slight daily intermittent rises in temperature which cannot be explained by any other observations. Frank evidence of bacterial endocarditis in the presence of syphilitic aortic insufficiency usually bespeaks the involvement of a valve other than the aortic.

The pathogenesis of bacterial endocarditis is discussed in relation to our 9 cases, and possible reasons for the infrequency of the simultaneous occurrence of syphilitic aortic valvulitis and bacterial endocarditis are presented.

Dr. Frank B. Kindell and Dr. John T. King Jr. aided in the preparation of this paper.

FURTHER EXPERIENCE WITH THE ROENTGEN DIAGNOSIS OF IDIOPATHIC STEATORRHEA

REPORT OF CASES, INCLUDING POSTMORTEM OBSERVATIONS IN ONE CASE

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In a recent paper [1] I reported 6 cases of so-called idiopathic steatorrhea, including roentgen examinations. The diagnosis of this symptom complex, which includes nontropical sprue, intestinal infantilism and celiac disease, was based on the following considerations: (1) Steatorrhea was demonstrated in each instance; (2) in the few cases in which the fat partition in the stools was determined, it was normal; (3) examination of the duodenal ferments in 1 case gave normal values; (4) in no instance up to the time of publication of the paper was there any clinical evidence of pancreatic involvement. In addition, in the 6 cases there were other clinical features generally assumed to accompany idiopathic steatorrhea, namely, anemia, flat blood sugar curve, tetany and low serum calcium. However, not all of these features were present in all the cases, nor were the features always constant in the same case.

Roentgenologically, there were noted changes in the bones, faint filling of the gallbladder, ileal stasis and colonic dilatation and redundancy; and, most striking of all, in 4 cases there was the peculiar smooth appearance of the upper part of the small intestine which I have described as the "moulage sign." This appearance was first reported by Snell and Camp,[2] in 1934. In 1 case there was, in addition to the "moulage" appearance, an intermittent dilatation with spasm in the loops of the small intestine, a phenomenon which had been previously described by Mackie, Miller and Rhoads,[3] in 1935. These findings were sufficiently distinctive to enable me to make a diagnosis of idiopathic steatorrhea on inspection of the roentgen films alone. In a recent conversation I learned that Dr. Walter C. Alvarez has had the same experience.

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2. Snell, A. M., and Camp, J. D.: Chronic Idiopathic Steatorrhea: Roentgenologic Observations, Arch. Int. Med. **53**:615-629 (April) 1934.

3. Mackie, T. T.; Miller, D. K., and Rhoads, C. P.: Sprue: Roentgenologic Changes in the Small Intestine, Am. J. Trop. Med. **15**:571-590, 1935.

Since writing the original paper I have observed 2 new cases, 1 of which I have had the opportunity of following to autopsy. In this instance it was possible to demonstrate complete loss of intestinal valvulae in the areas where the "moulage sign" had been observed; the anatomic basis of the sign was thus established. It is the plan of this paper to recapitulate briefly the 6 cases already reported, noting new developments where these have occurred, and then to report in detail the new material.

CASES PREVIOUSLY REPORTED

Case 1.—The patient was a woman aged 45 with a history of probable steatorrhea in childhood. There was marked dwarfing of the skeleton, with deformity of the bones and osteoporosis. During an "active period" observation at Montefiore Hospital showed steatorrhea, abdominal distention and a flat blood sugar curve. The "moulage sign" was not demonstrated.

Case 2.—A woman 55 years old gave a history of long-standing duodenal ulcer and of a ten year period of unexplained loss of weight, which had terminated in a recent phase of frothy diarrhea with marked abdominal distention. Death ensued from perforation of, and hemorrhage from, the ulcer. The combination of peptic ulcer with steatorrhea has been previously described in the literature and will be mentioned again in case 7. A "moulage sign" was demonstrated. The gallbladder was not studied.

Case 3.—A man of 30 suffered from marked malnutrition, with loss of almost half his normal body weight; achlorhydria; gastrospasm and pylorospasm, which led to exploratory laparotomy and gastrotomy; anemia; psychotic symptoms; tachycardia; hyperhidrosis, and asthenia. There were colonic dilatation and redundancy. The "moulage sign" was not demonstrated. The gallbladder was not studied. Through Dr. J. S. Diamond [4] it was learned that a subsequent study of the pancreatic secretion by the new secretin technic showed a diminution in the concentration of lipase to 32 units, as against a normal minimum of 153 units. Thus there is a possibility that this case may, after all, be one of pancreatic insufficiency rather than one of idiopathic steatorrhea. It should be observed in this connection that up to the present time it has been impossible to set definite quantitative limits for normal values for lipase, presumably because most of the studies reported were done on the mixed duodenal secretions (Comfort, Parker and Osterberg [5]) instead of on the pure pancreatic juice obtained by the new technic.[6]

4. Diamond, J. S.; Siegel, S. A.; Gall, M. B., and Karlen, S.: The Use of Secretin as a Clinical Test of Pancreatic Function, Am. J. Digest. Dis. **6**:366-372, 1939.

5. Comfort, M. W.; Parker, R. L., and Osterberg, A. E.: The Concentration of Pancreatic Enzymes in the Duodenum of Normal Persons and Persons with Disease of the Upper Part of the Abdomen, Am. J. Digest. Dis. **6**:249-254, 1939.

6. Ågren, G., and Lagerlöf, H.: The Pancreatic Secretion in Man After Intravenous Administration of Secretin, Acta med. Scandinav. **90**:1-29, 1936. Ågren, G.; Lagerlöf, H., and Berglund, H.: The Secretin Test of Pancreatic Function in the Diagnosis of Pancreatic Disease, ibid. **90**:224-271, 1936. Chiray, M., and Bolgert, M.: Le test à la sécrétine dans les affections du pancréas, Arch. d. mal. de l'app. digestif **29**:5-32, 1939. Diamond, Siegel, Gall and Karlen.[4]

CASE 4.—A woman aged 45 suffered from steatorrhea complicated by severe abdominal pain, hemorrhagic diathesis, anemia, tetany, amenorrhea, disturbed water metabolism, transient severe leukocytosis and increased coagulation time. Roentgen studies showed colonic dilatation and a "moulage sign" which persisted for over a year before appropriate therapy was instituted. After treatment for sprue the "moulage sign" diminished and there was clinical recovery. The gallbladder was atonic and filled faintly at the original examination. Hemorrhage into the digestive tract took place; this was unusual, but it had been previously reported in the literature by Holst [7] and Snell [8] and was again observed in case 7.

After the steatorrhea was controlled, pain developed in the left upper quadrant of the abdomen, which always came on in the late afternoon, evening or night. Pain is not usual in idiopathic steatorrhea but was observed again in case 7. Belladonna, alkalis and calcium had some effect on the pain, but the most reliable medicament was acetylsalicylic acid. Since the salicylates are known to be cholagogues this observation is interesting. After the original examination bile salts were administered for one month. The gallbladder was then restudied; it was found to be smaller in size, and the concentration of dye was greater.

CASE 5.—A woman aged 27 suffered from fatty diarrhea and malnutrition. Hypochromic anemia, which changed to a hyperchromic form during treatment, a low blood calcium and a typical flat blood sugar curve were found. The "moulage sign" was present for at least three years before specific treatment was started, but it practically disappeared after a month of management for sprue. Roentgenologic study of the gallbladder showed faint filling with dye. Since the time of the original report the patient has survived an attack of pneumonia, and in April 1939 she completed a normal pregnancy and labor.

CASE 6.—A single man 21 years old had steatorrhea with only mild diarrhea. The disease had been characterized by foul stools, occasional cramps and fever, intercurrent jaundice, considerable malnutrition, progressive secondary anemia, abdominal distention, sore tongue, pains in the legs, moderate osteoporosis and pigmented cutaneous lesions.

Roentgenologic examination showed a dilated colon and almost complete lack of filling of the gallbladder. The roentgen appearance of the small intestine was striking. The first two or three loops of the jejunum were normal, but the succeeding convolutions showed not only complete absence of valvulae but a remarkable segmentation, in which enormously dilated smooth segments were separated by spastic areas which caused temporary arrest in the passage of the barium sulfate.

Since the original report the patient has improved clinically to such an extent that he considers himself well. When last seen he weighed 155 pounds (70 Kg.) (a gain of about 27 pounds [12 Kg.] in all). Despite this clinical progress the appearance of the jejunum remained unchanged for three months after the original examination; it was not until March 13, 1939 (that is, nine months after the original observation) that a roentgen examination showed somewhat less dilatation and spasm of the upper jejunal loops. The progress of the barium through the small intestine was definitely more regular and more rapid. The stomach took four hours to empty instead of the three hours required on

7. Holst, J. E.: Ein in Dänemark aufgetretener Fall von Sprue, Acta med. Scandinav. **66**:74-99, 1927.

8. Snell, A. M.: Tropical and Nontropical Sprue (Chronic Idiopathic Steatorrhea): Their Probable Interrelationship, Ann. Int. Med. **12**:1632-1671, 1939.

previous occasions. In other words, there seemed to be a very gradual improvement in the pattern and function of the small intestine. This improvement, however, will need to be confirmed by further observation.

The examination of the gallbladder was repeated after eight and one-half months, and again there was almost complete lack of filling. The patient is now receiving bile salts.

NEW CASES

CASE 7.—A boy 9 years old was observed in the medical service at the Montefiore Hospital from Sept. 22, 1938 to Jan. 5, 1939.

History.—At two and one-half years of age the patient began to have two to three large stools daily. Two years later (1933) fever, abdominal distention, diarrhea and anemia were present. A clinical diagnosis of celiac disease was made about this time by Dr. Sidney V. Haas,[9] and enlargement of the liver and spleen were noted. The patient failed to cooperate in attempts to establish a dietary regimen proper for a person with celiac disease. In July 1937 the boy was admitted to the Lebanon Hospital because of vomiting and abdominal pain. There roentgenologic examination showed marked dilatation and spasm of the duodenum and jejunum, with absence of valvulae and delayed gastric emptying. These findings were interpreted as representing a partial obstruction due to congenital bands or inflammatory adhesions, but at exploratory laparotomy, on April 14, 1938, nothing was found but dilated loops separated by areas of intense spasm. The findings were subsequently interpreted as those of "intestinal tetany." Following the operation there were hematemesis and melena; a marked anemia developed, for which the patient received fifteen blood transfusions (300 cc. each) within a few months, without much improvement. At this time the boy began to present a serious behavior problem. He was noncooperative and complained of pain, for which no basis was evident and which was relieved by various procedures, including the injection of sterile water. On retrospect, however, it seems likely that the boy was actually suffering from intestinal spasm of greater or less severity and duration. At any rate, the pain never followed any special time pattern. There was no dysphagia. Unfortunately, it was never possible to impose any strict dietary regimen at any time, either in the hospital or at home.

In August 1938 the patient was admitted to Lincoln Hospital, where he was found to have dilatation of the esophagus as well as delayed gastric emptying.

On Sept. 22, 1938 the boy was admitted to Montefiore Hospital with the same complaints as in 1933—namely, fever, distention, diarrhea and anemia—plus hematemesis and melena.

Physical Examination.—There was much emaciation, the weight on admission being 17.7 Kg. (39 pounds). The height was 118 cm. (3 feet 10 inches). The abdomen was greatly distended (fig. 1). The liver and spleen were palpable. There was universal adenopathy, particularly marked in the groins, axillas and neck. The abdominal distention was attributed by some persons to ascites, but the fluid was probably all intraintestinal.

Laboratory Data.—On admission to the hospital the hemoglobin was 69 per cent. There were 4,710,000 red cells and 10,360 white cells; the differential count was normal. The erythrocyte sedimentation time was 10 mm. in one hour. The value for blood sugar was 99 mg. per hundred cubic centimeters; for urea

9. Haas, S. V.: Celiac Disease: Its Specific Treatment and Cure Without Nutritional Relapse, J. A. M. A. **99**:448 (Aug. 6) 1932.

nitrogen, 15.1 mg.; for cholesterol, 167 mg., and for cholesterol esters, 111 mg. (all these values are normal). A dextrose tolerance test was not made, nor were the gastric contents analyzed after a test meal.

An estimation of the fat in the stools during the diarrhea phase showed that 24 per cent of the total fat intake was being excreted. This is almost five times the normal loss of fat, which is usually given as 5 per cent of the amount ingested. A determination of the partition of fat in the stool could not be carried out.

Roentgen Findings.—Dr. J. Bower studied the bones (March 18, 1938) and found that the epiphyses corresponded to those of a child between 5 and 6 years of age.

On roentgen examination of the gastrointestinal tract (Oct. 31, 1938) I found that the esophagus was dilated and showed a fluid level. All films showed gas pockets and dilatation of the distal portion of the colon.

The stomach at first emptied rapidly into the duodenum, which was dilated and completely devoid of valvulae. For about a half-hour there was an occlusive spasm just proximal to the duodenojejunal angle. The barium sulfate meal then entered the greatly dilated jejunal loops, which were entirely smooth and had a

Fig. 1 (case 7).—Photograph of patient, showing extreme emaciation, enlarged abdomen and laparotomy scar.

marked "moulage" appearance (figs. 2 and 3). The proximal loops—that is, those in the left upper quadrant—retained the barium for about one and one-half hours. During this time the patient experienced pain, which persisted for one and one-half hours despite the administration of 15 minims (0.92 cc.) of tincture of belladonna and one-fifth grain (12 mg.) of codeine.

Two hours after the ingestion of barium the head of the column had reached the lower jejunal loops—that is, those in the left iliac fossa. At two and one-half hours the small intestine was filled to the right of the midline; this observation suggested that the ileum was now receiving the barium. At five hours the barium had left the jejunum, despite the fact that there was still a gastric residue. At the twenty-nine hour observation a small gastric residue persisted, despite the occurrence of vomiting in the interval.

The gallbladder was not studied.

Summary of Roentgen Findings.—The outstanding observations were as follows: dilatation of the esophagus; dilatation and segmentation of the duodenum and jejunum; absence of valvulae in the duodenum and jejunum ("moulage sign"); delayed gastric emptying; very irregular passage of barium through the small intestine, due to spasm.

Course.—For a while diarrhea and distention persisted, but soon these disappeared simultaneously and did not return. The diarrhea consisted of three to

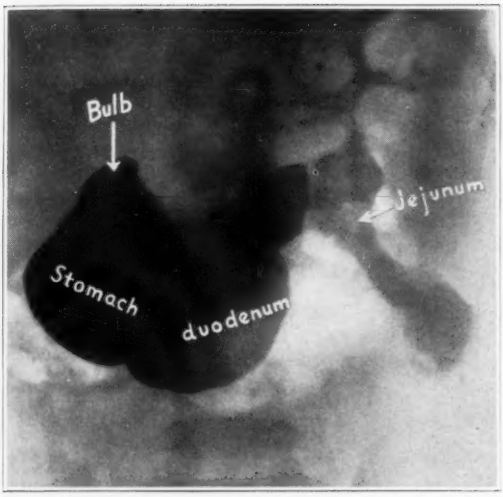

Fig. 2 (case 7).—Roentgenogram taken thirty-five minutes after ingestion of a barium sulfate meal, showing dilatation of the duodenum and occlusive spasm of the proximal portion of the jejunum with the "moulage sign" (loss of valvulae conniventes). Note that the meal has not progressed beyond the first loop of the jejunum.

Fig. 3 (case 7).—Roentgenogram taken forty-five minutes after ingestion of a barium sulfate meal (ten minutes after figure 2), showing sudden release of the spasm with resultant filling of the next few jejunal loops. Note the typical "moulage sign" and the dilatation and spasm.

four copious watery stools per day; later there was one mushy stool daily. The pain became localized in the left upper quadrant of the abdomen. It was still irregular in onset, and it was difficult to understand what controlled it. However, belladonna seemed to give more relief than other forms of medication.

An attempt was made to place the child on a diet appropriate for a person with sprue, and calcium, nicotinic acid, liver extract (parenterally) and vitamins were administered. For a time the patient gained weight (3 Kg. in all), but he always remained a most serious behavior problem. Much ground was lost owing to several recurrences of hematemesis and melena. The hemoglobin dropped as low as 20 per cent. Feeding was particularly difficult and ultimately required the use of an intragastric tube and the employment of special nurses. Regurgitation of food was frequent, and the weight ultimately dropped to 14.9 Kg. (33 pounds). Despite all efforts the condition became worse, and the lad succumbed to inanition and exhaustion on Jan. 5, 1939.

Autopsy.—The autopsy was conducted by the department of pathology of Montefiore Hospital.

The liver weighed 850 Gm. and measured 21 by 15 by 5 cm. Its capsule was smooth and glistening, and its color was purplish blue. On section, the surface was deep red; in some areas, particularly in the subcapsular region, the color was almost cyanotic. There was some distortion of the lobular structure, and there were numerous yellowish specks (1 to 2 mm. in diameter) throughout the parenchyma. Microscopically, the liver showed marked central congestion. There were numerous foci of fatty infiltration. The central veins were dilated and engorged. Several portal areas showed small collections of lymphocytes and polymorphonuclear cells.

The gallbladder was small and of normal shape; it contained about 30 cc. of golden brown bile. The bile ducts were patent and not dilated. There were no stones.

The pancreas weighed 38 Gm. On section, a normal lobular structure, with a fair amount of congestion, was noted. The pancreatic ducts were not dilated. Microscopic examination showed that the islets were small but not decreased in number. The acini were normal; the blood vessels were congested.

The spleen was grossly enlarged; it weighed 190 Gm. (its normal weight in adults is 100 to 120 Gm.), and it measured 14 by 8.5 by 3 cm. The capsule was glistening, and normal wrinkling was absent. On section, the surface was deep red and was fairly firm. There was an increase in fibrous stroma. The pulp did not scrape easily, and the follicles were indistinct. Microscopic examination disclosed that the lymph follicles were small and discrete; many contained fairly large cells with abundant clear-staining cytoplasm and large round clear nuclei with prominent nuclear membranes (histiocytes). The small vessels were thin walled. The pulp was congested, and there was diffuse hyaline fibrosis.

The adrenals were normal in shape but somewhat small (weight of both, 8 Gm.). On multiple section, the cortex appeared to be thin. The medullary portion was normal. Microscopic examination showed marked congestion. The zona glomerulosa and the zona fasciculata were very rich in lipoids. The inner cortical zone was rich in deep brown pigment. The periadrenal adventitia was congested and contained fat droplets with a pale blue mucoid matrix (hibernating).

The thymus was not present.

The first half of the esophagus was normal, but the distal half was dilated to twice the normal diameter and at the cardiac portion its lumen was constricted to a very small opening by a thick fibrous band which was continuous with the margin of the esophageal hiatus of the diaphragm. Immediately above this

constriction there was an ulceration in the mucosa, approximately 0.5 cm. in diameter. The floor of the ulcer was smooth and thickened, and the ulcer appeared to be healed. The regional lymph nodes were especially prominent. Microscopically, all layers and secretory glands were normal; there was perhaps some thickening of the skeletal muscle fibers.

The stomach was somewhat dilated. The mucosa was glistening and gray-brown. The rugae were prominent. Some pinpoint agonal hemorrhages were noted. There was an indentation at the midportion of the greater curvature of the stomach, and the omentum was drawn up at this point. Microscopic examination revealed hyperplasia of the mucous cells, numerous parietal cells and focal collections of lymphocytes, with a few plasma cells and eosinophils scattered through the tunica propria and the epithelial layer. There was congestion in the latter areas.

Examination of the small intestine showed the duodenum to be bile stained. The third portion of the duodenum and the first 2 feet (60 cm.) of the jejunum

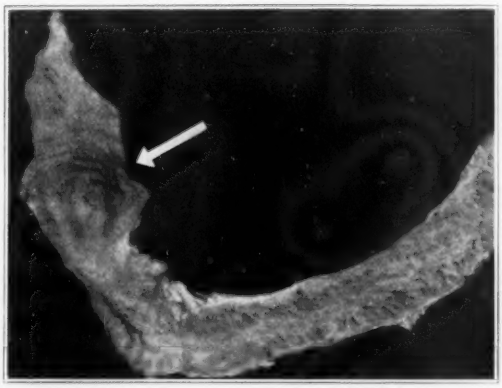

Fig. 4 (case 7).—Loop of jejunum showing dilatation with complete loss of valvulae on the left except for a tuft of large coarse folds at the left center (arrow). On the right the valvulae are almost normal.

were dilated to about twice the normal diameter. The mucosa was pink-gray, but extensive areas in this portion showed complete absence of the valvulae conniventes (fig. 4). The thinned areas of the jejunum were definitely pouched, and between such areas the mucosa was hypertrophic and thickened and the valvulae conniventes were accentuated. There were in this region, however, several small areas having valvulae of a peculiar circinate and serpiginous character. The distal portion of the jejunum had a normal structure, and this region and the ileum were not dilated. There was some enlargement of the mesenteric lymph nodes, especially marked in that portion of the mesentery containing the upper part of the jejunum. Microscopically, the mucosa of the duodenum appeared congested. There were some plasma cells and eosinophils in the tunica propria. Some desquamation of the epithelium was noted. There was no submucosal fat. The mucosa of the jejunum was congested and atrophied, with lymphocytic infiltration and connective tissue proliferation present, and it was covered by debris consisting of clumps of mucous cells and many plasma cells. There was congestion of the submucosa. The muscular layers were normal.

In several portions of the colon there was thinning of the wall, with pouching and with absence of normal haustrations. The appendix was normal.

Summary of Autopsy Observations.—The pancreas was normal, the spleen was enlarged and the adrenal cortex was narrowed. The lower part of the esophagus was dilated; there was a healed ulcer at the cardiac portion. The small intestine showed remarkable changes: The third portion of the duodenum and the first 2 feet of the jejunum were dilated to twice the normal diameter, and there were extensive areas in this region which showed complete absence of the valvulae conniventes. Microscopic examination of the denuded areas showed mucosal atrophy, with lymphocytic infiltration and connective tissue proliferation. Between the denuded spaces many of the valvulae were hypertrophied and misshapen. The regional lymph nodes were markedly hypertrophied.

Synopsis of Case.—A diagnosis of idiopathic steatorrhea was made in the case of a boy of 9 years who had been under observation by several physicians and in several hospitals since the age of 2½ years. Five years previously a clinical diagnosis of celiac disease had been made. An exploratory laparotomy had revealed "tetany" of the small intestine. The presenting symptoms were recurrent fatty diarrhea, fever, abdominal distention, recurrent gastrointestinal bleeding, hepatosplenomegaly and anemia. Roentgen examination showed typical "moulage" appearance of the duodenum and jejunum and marked dilatation alternating with spasm. There was progressive emaciation, and death from exhaustion. Autopsy showed a healed ulcer of the esophagus, an enlarged spleen, hypertrophied lymph nodes, a normal pancreas and narrowing of the adrenal cortex. The entire upper part of the small intestine was greatly dilated and was ballooned out in places. In the duodenum and jejunum complete atrophy of valvulae was demonstrated in the areas involved by the "moulage sign." This is believed to be the second recorded report of a case in which the roentgen appearance of the small intestine during life was confirmed by postmortem examination, and the first report in which the roentgen and postmortem protocols have been given in detail.

Case 8.—The patient, a single woman aged 47, was first seen Dec. 7, 1938, at which time she complained of diarrhea and a burning sensation in the abdomen.

History.—For years there had been attacks of abdominal distress, characterized by gas, a sensation of burning and, occasionally, nausea, which were attributed to "nerves." Twelve years previously a fibroid uterus and the appendix had been removed. For ten years there had been intermittent cramps in the legs, worse in winter. Four years previously she had fractured an arm by a fall. During the two weeks before admission there had been four to five frothy stools per day, and the tongue had been sore.

Physical Examination.—The patient was 4 feet 10¾ inches (149 cm.) in height and weighed 87 pounds (39.5 Kg.). Since the ideal weight for that height is 124 pounds (56.2 Kg.), her weight deficit was 37 pounds (16.8 Kg.). The tongue was smooth at the edges but showed no ulcers. The abdomen was distended and tympanitic. There was a bilateral carpal spasm on constriction of the upper arm (Trousseau sign) but no increased irritability of the facial nerve (Chvostek phenomenon).

Laboratory Data.—The feces were collected for three days while the patient was on a standard Schmidt diet, which included milk and contained 142 Gm. of fat per day. The total fat in the stools for the three day period was 127.7 Gm., a loss of 30 per cent of the fat ingested as against a normal loss of about 5 per cent. The fatty acids constituted 72 per cent of the total fat; this indicated that the action of the pancreatic ferments was normal.

Except for increased indican in the urine, the other laboratory data were normal. The blood was studied by Dr. N. Rosenthal. The values for hemoglobin and red cells were high normal figures, presumably because of the increased hemoconcentration. The serum calcium was 9.2 mg. and the phosphorus 3.1 mg. per hundred cubic centimeters. The sugar tolerance test was as follows (values in milligrams per hundred cubic centimeters):

Fasting specimen	97.4
One-half hour after 50 mg. dextrose (first dose)	136.0
One-half hour after 50 mg. dextrose (second dose)	130.5

The test meal showed a free acidity of 27 and a total acidity of 54 (normal figures).

Roentgen Findings.—On Dec. 8, 1938 the stomach was normal in size, shape, position, filling, tonus and peristalsis and was empty at five hours. The duodenal cap was complete. The remainder of the duodenum was greatly dilated and showed complete loss of valvulae ("moulage sign"). The jejunum was moderately dilated and showed coarseness or enlargement, rather than ironing-out, of the valvulae. The ileum seemed normal and was empty at nine hours. The filling of the colon was slightly accelerated, but its emptying was delayed; ninety-six hours and 4 stools were required to clear the barium. The opaque enema showed that it took 38 ounces (1,124 cc.) of liquid (normal amount) to fill to the cecum. The splenic flexure was redundant and diaphragmatic in position but movable. The cecocolon was dilated, but the colon as a whole did not show the tremendous dilatation which is a characteristic in cases of marked carbohydrate intolerance. The gallbladder did not fill with dye after it was administered by mouth, despite the absence of diarrhea at the time, but reexamination after one month of treatment with bile salts showed distinct filling, only slightly fainter than normal.

When the barium sulfate meal was repeated, on Dec. 22, 1938, the duodenum and jejunum appeared more normal than at the first examination.

The patient's hand and forearm were compared with those of her sister, two years younger, and they showed a slightly diminished density of the radius and phalanges.

Summary of Roentgen Findings.—In this patient the "moulage sign" was limited to the duodenum, the changes in the jejunum being minimal. Yet these findings seemed sufficient to suggest the diagnosis of idiopathic steatorrhea, which was confirmed by the examination of the stools. The only other important roentgen observation was the nonvisualization of the gallbladder, with subsequent visualization after treatment with bile salts.

Course.—The diet was arranged in accordance with the feeding plan used for patients with sprue, except that, in view of the normal blood sugar curve, carbohydrates were fed with relative freedom. The diarrhea recurred during the three days of milk drinking imposed by the Schmidt test. Otherwise, the bowels moved once and twice a day and the stools were normally formed. Heartburn was soon controlled, but the flatulence responded slowly to treatment. The odor of the flatus was foul. The cramps in the legs were relieved by administration of calcium. On February 15 the diet included protein, 113 Gm.; fat, 48 Gm., and carbohydrate, 422 Gm.; the total number of calories was 2,487. The patient was taking six to eight bananas daily. The weight had reached 99 pounds (44.9 Kg.) on May 3, 1939, a gross gain of 12 pounds (5.4 Kg.) in almost five months. The appetite and strength were much improved. The treatment consisted of restricted diet and medication with bile salts.

Synopsis of Case History.—The patient was a short woman of 47, whose weight was 30 per cent below normal. There was a positive Trousseau phenomenon. The roentgen study revealed that the "moulage sign" was limited to the duodenum and that the jejunum was involved slightly if at all. After the ingestion of dye the gallbladder did not visualize on the first examination; but reexamination after one month of treatment with bile salts showed a fairly dense concentration of dye.

COMMENT

Correlation of Roentgen and Postmortem Examinations.—The present study shows that the changes seen roentgenographically in the small intestine in *advanced* idiopathic steatorrhea are based on loss or destruction of the valvulae conniventes and dilatation and thinning of the intestinal wall. This has been proved objectively by autopsy in a case in which roentgen examination during life showed the "moulage sign," together with segmentation and dilatation of the duodenum and jejunum. The results of autopsies recorded in the literature for similar cases have been extremely variable (Thaysen,[10] Fairley [11]). Loss of valvulae and thinning of the colonic wall have been found by some investigators but not by others. In only one previous instance, apparently, have roentgen studies been correlated with postmortem studies. This was a case, reported by Mendez Ferreira and Bargen,[12] in which the roentgen examination showed loss of valvulae and clumping of the barium in elongated masses, more marked in the ileum than in the jejunum. The results of postmortem examination were not given in detail; but there were atrophy of the mucosa and edema of the submucosa. The latter was particularly marked in the ileum, where, in addition, the Peyer patches showed atrophy.

That in advanced stages the intestinal tract may be damaged to a point where irreversible changes have occurred seems to be clear from the observations made in case 7. A similar opinion has been voiced by Snell.[8]

Just what anatomic changes accompany *less severe* forms of the disease is still undetermined. Mackie, Miller and Rhoads [8] studied sections of the small intestine in cases of ulcerative colitis associated with deficiency disease. They stated the belief that in their cases intestinal abnormalities similar to those of sprue had been shown by roentgen examination; and in their histologic preparations they noted edema of the mucosa and submucosa and slight infiltration of mononuclear wan-

10. Thaysen, T. E. H.: Non-Tropical Sprue, Copenhagen, Levin & Munksgaard, 1932.

11. Fairley, N. H.: Sprue: Its Applied Pathology, Biochemistry and Treatment, Tr. Roy. Soc. Trop. Med. & Hyg. **24**:131-179, 1930.

12. Mendez Ferreira, A. E., and Bargen, J. A.: So-Called Nontropical Sprue Associated with Tuberculosis of the Lymph Nodes, Proc. Staff Meet., Mayo Clin. **12**:289-294, 1937.

dering cells and lymphocytes. In this connection the reversibility of the mucosal alterations is again of practical interest. In less advanced disease, such as was present in cases 4, 5 and 8 of the present series, it has been shown that with proper treatment the "moulage sign" may disappear, or at least regress. This phenomenon, which suggests that the valvulae conniventes are restored to normal, has also been observed by Snell and Camp [2] and by Mackie, Miller and Rhoads.

The next question that arises is what happens in cases in which the degree of severity of the disease is intermediate. These are characterized by the presence of dilatation, as shown by roentgen examination, in spite of which recovery takes place. Case 6 is such an instance. Here the dilatation was marked, but, unlike the patient in case 7, who died, the patient improved steadily; and there is at present some evidence that the bowel is slightly less abnormal than it was at first. Only time can tell how far the improvement, as seen roentgenographically, will go.

To summarize the factors in regard to prognosis, it may be stated that in the mild form of the disease, in which the "moulage sign" is the only positive roentgen sign, the progress of the disease is reversible; but that in advanced disease, in which dilatation and atrophy of the wall of the bowel have supervened, a restitutio ad integram, though perhaps still possible, is not very likely.

That the duodenum may be the only site of the "moulage sign" is demonstrated by the observations in case 8 of the present series. Up to that time the jejunum had been the chief site of involvement noted in my cases.

Practical Value of "Moulage Sign" Confirmed.—My experience so far has confirmed the clinical impression that in so-called idiopathic steatorrhea the significant, if not the only, abnormality, is disturbance in absorption by the small intestine. In the only case in this series in which autopsy was done the pancreas was anatomically normal. This supports the view that idiopathic steatorrhea, which includes celiac disease, is to be sharply distinguished from the congenital steatorrhea, due to cystic fibrosis of the pancreas, recently described by Andersen [13] in this country and by Harper [14] in Australia. I believe that the roentgen signs are of practical value, even though my original statement may have to be modified by further experience, particularly in view of the fact that cases of known pancreatic disease have not yet been available to me for comparative study.[15]

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13. Andersen, D. H.: Cystic Fibrosis of the Pancreas and Its Relation to Celiac Disease: A Clinical and Pathologic Study, Am. J. Dis. Child. **56**:344-399 (Aug.) 1938.

14. Harper, M. H.: Congenital Steatorrhea Due to Pancreatic Defect, Arch. Dis. Childhood **13**:45-56, 1938.

15. Snell has just reported that he observed similar roentgen phenomena in 3 cases of pancreatogenous diarrhea; but this disease seems to be much less common than idiopathic steatorrhea.

Role of Biliary Tract in Idiopathic Steatorrhea.—The failure of the gallbladder to fill with dye in idiopathic steatorrhea has been further confirmed. Case 8 is the fourth consecutive case in which the gallbladder either failed to visualize or did so very faintly. Unfortunately, in no case was it practical to make a control examination after the intravenous injection of the dye. This procedure would help to prove whether the nonfilling is due to failure of the intestines to absorb the dye or to some associated disease of the biliary tract. The latter possibility has been suggested by Pillai and Murthi [16] and, more recently, by Hopman.[17] Radl and Fallon [18] also report a case of nontropical sprue in which the gallbladder was not visualized. Improvement in function of the gallbladder, as determined roentgenologically, followed the oral administration of bile salts in the 2 cases in which follow-up studies were available. The observation in case 4 that pain was best relieved by acetylsalicylic acid, a known cholagogue, may also be considered as suggestive evidence that an abnormal biliary status may be associated in some way with idiopathic steatorrhea. Clinically, the use of bile salts seems justifiable in the treatment of idiopathic steatorrhea.

Role of Adrenal Cortex in Idiopathic Steatorrhea.—The thinning of the adrenal cortex in case 7, in the presence of lymphatic hypertrophy and splenomegaly, seems to support the theory that insufficiency of the adrenal cortex may play a role in the etiology of idiopathic steatorrhea. In his recent monograph, Verzar [19] has advanced the theory that the capacity of the intestine to absorb fats and carbohydrates is closely associated with the activity of the adrenal cortex. Decreased activity of the adrenal cortex is apparently responsible for lack of absorption; and, experimentally, replacement therapy aids absorption. Dr. David Perla, of the department of pathology of Montefiore Hospital, was asked to discuss the significance of the autopsy observations in case 7 from this point of view; he replied as follows:

> The thinning of the cortex of the adrenal, in spite of the deposition of lipoid, may mean a decreased activity of the cortex. The presence of lipoid does not necessarily reflect the state of activity of the gland. It is not possible to state definitely from the histologic observation whether the adrenal cortex is in an exhausted state, since in all cachectic states lipoids are apt to increase in the adrenal cortex. Such increases do not, however, indicate an increase in cortical hormone but rather point to some type of storage of cholesterol.

16. Pillai, M. J. S., and Murthi, K. N.: Further Observations on the Radiological and General Findings in Sprue, Calcutta M. J. **30**:225-230, 1935.

17. Hopman, B. C.: Etiology of Tropical Sprue and Related Disease, Geneesk. tijdschr. v. Nederl.-Indië **78**:904, 1938; abstracted, J. A. M. A. **111**:214 (July 9) 1938.

18. Radl, R. B., and Fallon, M.: Nontropical Sprue with Duodenal Involvement and Tetany, Arch. Int. Med. **50**:595-604 (Oct.) 1932.

19. Verzar, F.: Absorption from the Intestine, New York, Longmans, Green & Co., 1936.

However, the presence of marked lymphoid hyperplasia and of splenomegaly with enlargement of the lymphoid follicles of the spleen is strongly suggestive of diminished activity of the adrenal cortex. Experimentally, removal of the adrenal glands is followed by pronounced hyperplasia of the lymphoid tissue and a regeneration of the thymus as well as by enlargement of the spleen. In the presence of an exhausting disease, especially of idiopathic steatorrhea, in which there is an additional factor of dehydration due to diarrhea, one would expect marked exhaustion of lymphoid tissue and atrophy of the thymus and of the spleen. The presence of the reverse, therefore, is strongly suggestive of a factor of adrenal cortical insufficiency in the pathogenesis of idiopathic steatorrhea.

In short, the observations at autopsy in this case lend some support to the theory that insufficiency of the adrenal cortex may in some way be associated with idiopathic steatorrhea resulting from failure of intestinal absorption.

Occurrence of Pain and Hemorrhage in Idiopathic Steatorrhea.—Pain and hemorrhage are not usually described in idiopathic steatorrhea, but in 2 of the cases so far observed they were prominent complications. The pain has been ascribed to intestinal spasm, although atypical left-sided biliary (gallbladder) colic may also possibly play a role in this connection. The nature of the bleeding is not clear. Holst [7] reports a case of this sort and so does Snell.[8] Coincidental "peptic" ulceration cannot be excluded (case 7). Another possible cause is some failure of coagulation of the blood (case 4) possibly due to lack of absorption of calcium or essential vitamins (vitamin K) or to insufficiency in biliary secretion. In fact, Snell has just reported that in 1 of his cases the prothrombin content of the plasma was reduced by more than 50 per cent.

SUMMARY

The 6 cases originally reported as instances of idiopathic steatorrhea have been summarized and brought down to date.

Reports of 2 new cases are presented. One of these is believed to be the first in which a detailed description is given of postmortem examination which confirmed the characteristic roentgen findings in idiopathic steatorrhea. In this case roentgen examination showed a marked "moulage sign" plus dilatation and segmentation of both the duodenum and the jejunum; postmortem examination showed that these were the sites of complete loss of the valvulae conniventes. The second case suggested that the "moulage sign" may be limited to the duodenum, with little if any involvement of the jejunum.

Evidence is gradually accumulating concerning the reversibility of the intestinal changes in idiopathic steatorrhea. In the mild form of the disease, in which only the "moulage sign" is present, the changes seem to be reversible. In far advanced stages with superadded segmentation and dilatation, a complete restitutio ad integram seems unlikely.

Further experience with the roentgen study of the small intestine shows that this method is of value in the demonstration of steatorrhea. Whether the characteristic intestinal changes are specific for idiopathic steatorrhea, as was originally believed, or whether they are also present in other forms of steatorrhea remains to be determined.

There is increasing evidence that the biliary tract may play an etiologic role in idiopathic steatorrhea. Failure of the gallbladder to fill with dye in the normal way continued to occur in those cases in which the gallbladder was studied roentgenologically.[20] Whether this phenomenon is due to impaired intestinal absorption or to some other cause is still undetermined. The administration of bile salts seems to improve the function of the gallbladder. Since bile salts are believed to aid in the absorption of fat, their use is tentatively recommended in the clinical management of idiopathic steatorrhea.

Bleeding and pain may occur in cases of idiopathic steatorrhea.

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20. More recent experience has shown that the gallbladder may visualize quite normally in some cases of idiopathic steatorrhea.

GENERALIZED SARCOIDOSIS OF BOECK

A CLINICAL REVIEW OF ELEVEN CASES, WITH STUDIES OF THE BLOOD AND THE ETIOLOGIC FACTORS

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DURHAM, N. C.

The opportunity of following 11 instances of generalized Boeck's sarcoid over a period of several years has presented unusual chances to study the progress of the disease from the clinical, metabolic and etiologic viewpoints. The clinical aspects of the disease have been discussed by numerous authors,[1] and Hunter [2] has presented a full historical review. A great variety of syndromes which resemble sarcoid probably can be grouped together.[3]

Little has been written on the metabolic changes associated with the disease. The relation of calcium metabolism to the cystlike osseous lesions and of protein metabolism to the activity of the disease and to lesions in the liver have been discussed.[4]

Etiologic studies in the past have been directed chiefly toward the demonstration of tubercle bacilli in the lesions. The use of various animals, usually guinea pigs and to a less extent rabbits and pigeons, has given disappointing results. Smaller animals, such as mice and rats, rarely have been used, in spite of the fact that rats react with a sarcoid-like lesion to tubercle bacilli and do not become allergic to tuberculin.[5] Cultural studies have resulted in the inconstant observation of a

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From the Department of Medicine, Duke University School of Medicine and Duke Hospital.

1. (*a*) Longcope, W. T., and Pierson, J. W.: Boeck's Sarcoid (Sarcoidosis), Bull. Johns Hopkins Hosp. **60**:223, 1937. (*b*) Schaumann, J.: Lymphogranulomatosis Benigna in the Light of Prolonged Clinical Observations and Autopsy Findings, Brit. J. Dermat. **48**:399, 1936.

2. Hunter, F. T.: Hutchinson-Boeck's Disease (Generalized "Sarcoidosis"): Historical Note and Report of a Case with Apparent Cure, New England J. Med. **214**:346, 1936.

3. Pinner, M.: Non-Caseating Tuberculosis: An Analysis of the Literature, Am. Rev. Tuberc. **37**:690, 1938.

4. Harrell, G. T., and Fisher, S.: Blood Chemical Changes in Boeck's Sarcoid with Particular Reference to Protein, Calcium and Phosphatase Values, J. Clin. Investigation **18**:687, 1939.

5. Jadassohn, W.: L'origine tuberculeuse de la maladie de Boeck, Bull. Soc. franç. de dermat. et syph. **41**:1344, 1934.

variety of organisms.[1b] Longcope and Pierson[1a] have attempted to grow fungi from the lesions on Sabouraud's medium but have had no success. Serologic studies with the organisms recovered from lesions and with stock strains of tubercle bacilli have been made by Schaumann.[1b] Little attempt to apply similar methods to fungi has been made

TABLE 1.—*Distri*

	Case 1 Age, 26 Negro Male			Case 2 Age, 23 Negro Female	Case 3 Age, 27 Negro Female			Case 4 Age, 2 Indian Male	
Date	8/1/34	12/11/34	10/14/38	6/9/36	12/3/36	10/28/37	9/15/38	3/16/37	9
Duration	4 mo.	8 mo.	4 yr.	12 mo.	7 yr.	8 yr.	9 yr.	12 mo.	
Activity	A	A	I	A	A	A	A	A	
Weight loss	27 lbs.	30 lbs.	15 lbs.	15 lbs.	30 lbs.	23 lbs.	.....	20 lbs.	
Temperature peak (Centigrade)	37.2	38.3	....	37	38.3	....	....	37.6	
Skin									
Nares	..	..	..	..	..	..	..	..	
Lids	+	+	..	+	..	..	..	..	
Head	..	+	..	+	..	+	Scars	..	
Trunk	..	..	..	++	+	+	Scars	..	
Extremities	..	..	Scars	++	+	..	Scars	..	
Perineum	..	..	..	..	..	..	..	..	
Mucous membranes	+	..	..	..	..	..	..	..	
Lymph nodes									
Auricular	..	..	+	..	..	..	+	+	
Mandibular	+	..	..	..	++	++	++	+	
Cervical	++	++	..	..	++	++	++	++	
Epitrochlear	..	+	..	..	+	..	..	+	
Axillary	..	++	..	..	+	+++	++++	++	
Inguinal	+	+++	..	..	+++	++++	++++	++	
Mediastinal	++	++	..	..	+++	+++	+++	++	
Others	..	..	..	..	++	++	++	+	
Other locations									
Lung	+++	++++	Clear	+++	±	±	±	0	
Rales	+	..	0	0	0	..	0	+	
Bone	..	0	0	±	++	++	+++	0	
Eye	0	0	Scars	0	0	±	0	++	
Tonsils	+	..	+	+	..	..	..	..	
Liver	+	0	..	0	0	+	0	0	
Spleen	0	..	0	0	0	..	+	0	
Miscellaneous	Muscle, orbit	Parotid, pharynx	Epididymus	..	..	Lacrimal	Parathyroid ?	..	
Biopsy									
Skin	..	..	..	+	+	..	..	..	
Node	..	+	..	..	+	..	+	+	
Other	Muscle	Parotid	..	..	..	..	..	..	
Treatment	Rest, cod liver oil			Rest, cod liver oil, neoarsphenamine for syphilis	Ultraviolet radiation	Intravenous typhoid vaccine	..	Cod liver oil, ultraviolet radiation, neoarsphenamine	
Result	Worse	Gaining weight	Well for 2 years	Slight improvement in 27 mo.		Improved, best for 2 years	Nodes growing		

previously in etiologic studies. The use of cutaneous tests has been confined to reactions to tuberculin and the interesting unconfirmed reaction to excised tissue of human beings, reported by Williams and Nickerson,[6] and this work has been repeated on the patients reported here, extracts of lymph nodes being used instead of skin. Allergic

6. Williams, R. H., and Nickerson, D. A.: Skin Reactions in Sarcoid, Proc. Soc. Exper. Biol. & Med. **33**:403, 1935.

studies have been done only in regard to the proteins of the tubercle bacilli.

The pathologic changes in surgical material have been described many times, and instances of sarcoid observed at autopsy have been reported with complete studies by Schaumann [1b] and Nickerson.[7] Excel-

Lesions

Case 5 Age, 27 Negro Male		Case 6 Age, 21 Negro Male	Case 7 Age, 27 Negro Female			Case 8 Age, 36 White Male	Case 9 Age, 32 Negro Female		Case 10 Age, 30 Negro Male	Case 11 Age, 30 Negro Male
2/37	4/27/39	6/16/37	6/14/38	10/18/38	5/18/39	8/16/38	11/7/38	5/26/39	2/24/39	4/4/39
mo.	2 yr.	18 mo.	10 wk.	7 mo.	1 yr.	4 mo.	6 yr.	6½ yr.	9 yr.	5 yr.
A	I	A	A	A	A	A	A	A	A	A
lbs.	0	..	25 lbs.	16 lbs.	0	40 lbs.	0	0	25 lbs.	0
3.5	37	36.9	39.2	37.4	37.5	37.5	37.4	37.6	38	38.2
..	..	+	..	..	..	..	+++	+++	..	+++
..	..	+	..	..	..	..	++	+++	..	+
..	+	+	..	..	..	..	++	++	..	+++
..	+	..	..	..	..	+	++	++	..	+
..	..	..	..	..	..	..	++++	++++	..	+
..	..	+	..	..	..	..	++	++	..	++
..	..	..	..	..	..	..	..	..	..	+
+	..	+	..	..	+	+	..	..	..	..
++	+	..	+	..	+	+	..	..	+	+
+	..	+	++	++	+	++	..	..	+	++
++	..	..	+	..	..	+	..	..	+	++
++	..	+	+	+	+	+	..	+	++	+
+++	..	+	++	++	+	+	..	..	++	+
+	+	+	++	+++	++	..	±	..	±	..
+	..	+	..	++	..	+	..	..	..	++
0	0	0	0	0	0	+++	++	++	+++	+++
..	0	..	0	..	0	0	0	0	+	+
0	0	0	..	0	0	±	0	0	±	+
0	0	0	0	0	0	0	0	0	+	0
..	..	..	..	..	..	+	..	..	..	..
0	..	..	±	0	+	+	0	±	0	0
..	..	..	0	..	+	+	0	±	0	0
..	..	..	..	..	..	..	..	..	..	Pharynx
..	..	++	..	..	..	..	+	..	..	+
++	..	+	+	+	..	+	..	..	++	+
..	..	..	..	..	..	..	..	..	..	..
ntra-enous ections asphen-mine, 6 Gm.	..	Cod liver oil	Rest, cod liver oil	Cod liver oil	..	Rest, cod liver oil	Ultraviolet radiation		Rest, cod liver oil, antisyphilitic treatment	1,360 roent-gen units
..	Well in 21 mo.	..	..	Gaining weight	Nodes unchanged	..	No improve-ment	..	..	..

lent reproductions of roentgenograms of the chest and of bones [8] are available. The hematologic picture and an increase in the sedimentation

7. Nickerson, D. A.: Boeck's Sarcoid: Report of Six Cases in Which Autopsies Were Made, Arch. Path. **24**:19 (July) 1937.

8. Snapper, I., and Pompen, A. W. M.: Pseudo-Tuberculosis in Man, Haarlem, de Erven F. Bohn, 1938.

rate have been recorded in some instances. Electrocardiographic changes have been described [9] but are not specific.

These varied data are recorded for different groups of patients. All the changes rarely have been followed in a single group of patients suffering from Boeck's sarcoid. The present etiologic studies were undertaken to obtain additional data by using: (1) species of animals not used by others in the attempt to isolate acid-fast organisms; (2) cutaneous tests, cultures and serologic tests for fungi and other organisms, and (3) the cutaneous test of Williams and Nickerson. Metabolic studies

Fig. 1 (case 9).—Patient with nodules on the eyelids and destruction of the nares.

were directed toward: (1) the relation of the cystlike osseous lesions to calcium, phosphorus and phosphatase activity and the occurrence of abnormal proteins in the urine; (2) the location of the lesion responsible for the hyperglobulinemia, and (3) the variations in the concentration of constituents of the blood with changes in the activity of the lesions.

CLINICAL DATA

The present series of patients with the generalized form of Boeck's sarcoid, composed of 11 patients observed since 1934, is the largest yet

9. Salvesen, H. A.: The Sarcoid of Boeck: A Disease of Importance to Internal Medicine, Acta med. Scandinav. **86**:127, 1935.

reported in the United States and is the first from the South. The series reported by Longcope and Pierson [1a] is the only other group in which Negroes predominated; the disease has not been previously reported as occurring in the American Indian. The occurrence primarily in young adults is in accord with the experience of others. Two cases, in which the disease was of five and twenty-seven months' duration, respectively,

Fig. 2 (case 9).—Generalized distribution of cutaneous lesions.

have been restudied twenty-one and twenty-nine months after clinical recovery. The condition in the majority of the cases in the literature is of relatively long duration; it is possible that cases in which the condition is of short duration have been overlooked or wrongly diagnosed in the past.

The distribution of the lesions in the body is given in table 1. Lesions of the skin were the predominant ones in 4 cases and generally were in

the form of painless papules 1 to 5 mm. in size, with no surrounding erythema, induration or anesthesia; they occurred most frequently on the face, arms and legs. The skin was dry, and the lesions tended to have small scales or crusts but did not itch or become purulent. The occurrence along the margin of the eyelids should be especially emphasized, for this phenomenon is infrequent in other diseases involving the skin (fig. 1). Destruction and distortion of the nares was prominent in 2 instances (fig. 1). In 2 cases almost the entire body was involved, but the palms and soles were spared; the lesions were of varied shapes, ranging from annular to circinate (fig. 2). Lesions were occasionally

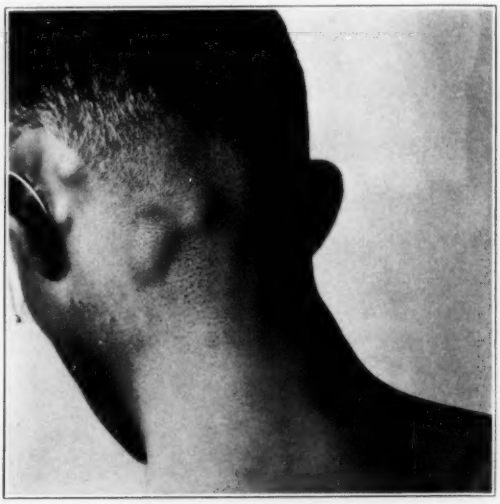

Fig. 3 (case 4).—Patient with enlargement of postauricular, posterior cervical and occipital lymph nodes.

noted in the scalp, on the mucous membranes and around the rectum or perineum.

Enlargement of the peripheral lymph nodes was the most prominent feature in 5 cases and occurred in all but 2 of the other cases. The nodes ranging up to 4 by 6 cm. in size were firm, rubbery, discrete, movable and painless, though painful nodes were present in case 5. Usually all the nodes were enlarged, though some groups were more prominent than others; enlargement of the epitrochlear, submental, preauricular and postauricular nodes should be emphasized (fig. 3). Enlargement of nodes along the borders of the muscles of the shoulder girdle or along the course of the major lymphatic vessels of the arm is rarely observed

in other conditions. Schaumann has emphasized that even the small nodes will show lesions when excised, and I have observed this generally to be true.

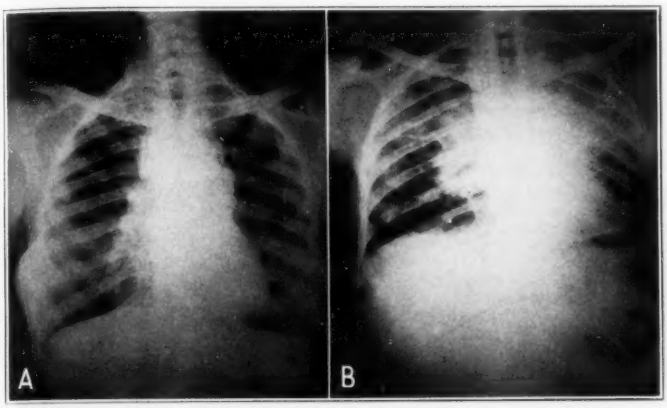

Fig. 4.—*A* (case 3), peribronchial fibrosis and enlarged mediastinal lymph nodes; *B* (case 10), diffuse infiltration in the central part of the lungs, sparing the apexes.

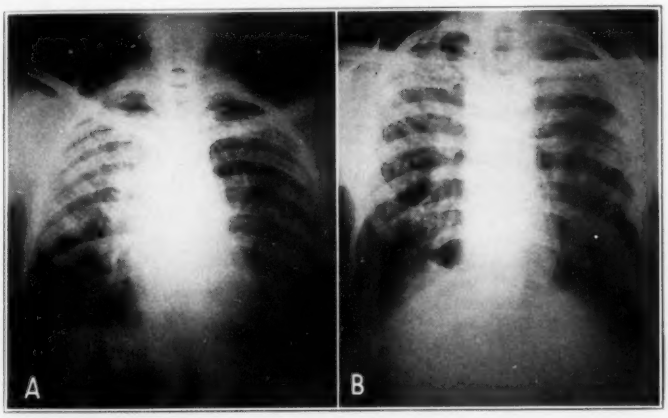

Fig. 5.—*A* (case 1), miliary infiltration, acute phase; *B* (case 11), generalized diffuse fibrosis, most marked in the central portion of the lung.

Distinction should probably be made between enlargement of the peripheral and that of the mediastinal nodes, for the latter often accompany lesions of the lungs and may occur with only moderate peripheral enlargement (fig. 4 *A*). Lesions in the lung fields were of three types: (1) peribronchial fibrosis and thickening, usually extending downward

symmetrically into the lower lobes (fig. 4 *A*); (2) soft infiltration in the midlung fields sparing the apexes (fig. 4 *B*), and (3) areas resembling miliary tuberculosis, with a fine marbled or reticulated appearance (fig. 5 *A*). In case 1 extensive miliary areas radiating from the hili completely disappeared, and four years later only slight peribronchial thickening remained (fig. 6). No essential change in the lungs has occurred in 3 other patients who have had serial roentgenograms taken over periods greater than one year. Rales were heard in 4 instances, while friction rubs were audible once. Pain in the chest, usually without physical signs, was a frequent symptom and occurred as a rule in the axilla or under the scapula.

Roentgen ray studies of the bones were made, as shown in table 2. Trabeculation and cyst formation in the hands and feet (fig. 7) and

TABLE 2.—*Roentgen Ray Stu*

	Case 1			Case 2	Case 3			Case 4
Date	8/1/34	12/11/34	10/14/38	6/9/36	12/3/36	7/6/37	10/13/37	9/2
Bones								
Hands	..	..	0	±	+++	+++	+++	
Feet	..	..	..	..	++	..	++	
Long bones	..	0	..	..	..	..	+	
Skull	..	..	..	..	±	0	..	0
Spine	..	..	..	..	0	..	0	
Pelvis	..	..	..	..	0	..	0	
Ribs	0	0	0	0	0	0	0	0
Chest								
Swollen nodes	++	..	0	..	++	+++	+++	
Peribronchial thickening	..	..	±	..	+	+	+	+
Infiltration of the middle portion of the lungs	..	..	..	+++	..	..	..	
Miliary areas	+++	++++	0	..	..	..	..	

cysts of the tibia, ulna and cuneiform bone were seen. The cystlike lesions appeared to be sharply punched out, with little change in the density of the surrounding bone; pathologically these areas are composed of sarcoid tissue in bone. Progression was noted over a period of two years in the cysts of the toes in case 3. Except for areas suggesting rarefaction in the ribs and decalcification in the hands, each noted once, no change was found in the bones of any of the other patients. Schaumann has pointed out that the degree of bone marrow involvement cannot be judged by the roentgen ray observations, for foci of involvement can be found by pathologic examination of the tissue when none appear in the films.

Longitudinal ridging of the nails occurred in 1 case (fig. 8). The lesion apparently is associated with changes in the bones and hence probably with actual invasion of the nail bed as well as interference with its blood supply. The nails are often brittle, even though no ridging is apparent. The tips of the fingers are often misshapen, and the skin

over the base of the nail, atrophic and shiny. The same changes may occur in the toes.

Invasion of the eye, producing iridocyclitis and keratitis, occurred in case 4. Under the slit lamp the yellowish white irregularly shaped opacities in the cornea resolved into numerous discrete "mutton fat" amorphous deposits on Descemet's membrane. They cleared up over a period of eighteen months, though the lesions elsewhere in the body showed no regression. Patient 1 showed no nodules in the eye when he was first seen, but scars were present four years later. In case 10 there had been an iridectomy six years previously, supposedly because of a syphilitic iritis which did not respond to antisyphilitic therapy; the condition may have been sarcoid at that time. The invasion of the lids noted in 5 cases has been mentioned; the periorbital tissues at the canthus of

Bones and the Chest

Case 4		Case 5		Case 6	Case 7			Case 8	Case 9		Case 10	Case 11
37	9/29/38	5/3/37	4/27/39	7/16/37	6/14/38	10/17/38	5/19/39	8/16/38	11/7/38	5/26/39	2/27/39	4/4/39
	0	0	0	0	..	0	..	±	0	..	0	+
	..	..	0	..	..	..	±	6	..	0	0	+
	..	..	..	..	..	..	..	0	..	..	..	..
	..	..	..	..	..	..	..	0	..	..	..	..
	..	..	.	..	0	..	..	..	..	..	..	..
	..	..	..	..	0	..	..	..	..	..	..	..
	0	0	0	0	0	0	0	0	0	0	±	0
	++++	++	+	++	++	+++	++	..	±	±	±	..
	..	..	+	++	..	+	+	..	..	..	..	..
	++	..	..	+	..	..	..	+++	..	..	+++	+++
	..	..	..	..	..	..	..	..	++	++	..	..

the eye were invaded once and the lacrimal gland was enlarged in 1 instance.

The skeletal muscles were extensively invaded in case 1 (fig. 9). A transient paralysis of the left internal rectus muscle was noted, probably due to invasion of this muscle, though invasion of nerve tissue cannot be excluded. Nodules were noted along the epididymis in 1 instance.

Occasional enlargement of the liver and spleen without jaundice or ascites was noted. Although Schaumann stated that abnormalities of the tonsils occurred in a large percentage of the cases, I noted only occasional enlargement. Involvement of the nasal septum was not found. In addition to patient 1, in whom the parotid gland was invaded, a 27 year old Negress, not studied in sufficient detail to be included in this series but with the diagnosis proved by biopsy, presented the typical picture of uveoparotid fever.[9a]

9a. This case was subsequently reported as case 6 of Thompson, W. C.: Uveoparotitis, Arch. Int. Med. **59**:646 (April) 1937.

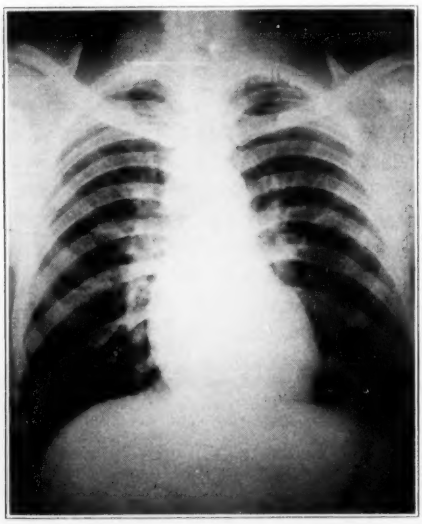

Fig. 6 (case 1).—Rontegenogram showing residual peribronchial fibrosis, taken four years after figure 5 *A*.

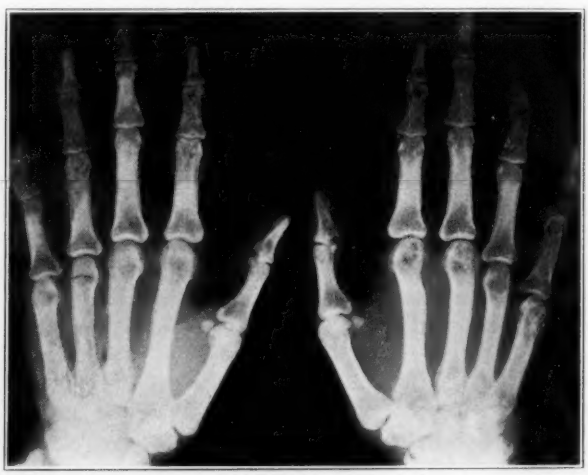

Fig. 7 (case 3).—Trabeculation and formation of cystlike lesions in the fingers.

Accentuation of the pulmonic second sound was noted in 2 cases in which the condition was of long duration, and there was splitting of the sound in others. This observation was interpreted as evidence of developing pulmonary hypertension because of the fibrosis in the lungs. Early clubbing of the distal phalanges was noted in only 1 instance.

Among the symptoms noted were weakness and fatigability, anorexia, loss in weight, pains in the joints, muscular stiffness, cough and pain in

Fig. 8 (case 3).—Longitudinal ridging of the nail and bulbous swelling of the middle phalanx.

the chest. Loss in weight, ranging up to 40 pounds (18 Kg.) in five months, occurred in all but 1 patient. Cough and transient pains in the chest often were present in the absence of demonstrable lesions in the lungs. Pains in the joints were usually not accompanied by demonstrable lesions. Fever was conspicuously absent; only rare observations above 38 C. were made. Few patients had noted fever at home.

PATHOLOGIC OBSERVATIONS

The most striking pathologic observation was the complete absence of inflammation in the tissues surrounding the lesions. In only 1 instance was the capsule of the lymph node found thickened or adherent to adjacent structures. The biopsy incisions healed promptly in all cases but 1, and in that case healing followed the removal of a buried suture.

Fig. 9 (case 1).—Section of acute lesion of the muscle showing giant cell with vacuoles, moderate lymphocytic infiltration of the tubercle and no surrounding or perivascular inflammation (× 110).

No necrosis was noted in the gross specimens. The lesions often were yellow before fixation.

Microscopically, the lesions were composed of groups of epithelioid cells, usually arranged in round forms resembling tubercles. In lymph nodes this reaction usually completely replaced the lymphoid tissue without involvement or thickening of the capsule. Small areas of necrosis

were occasionally observed in the centers of the tubercle-like lesions. Little fibrosis was found between the collections of tubercles, but in the lesions of long duration the connective tissue present was often hyalinized (fig. 10). Congo red stains for amyloid on such tissue occasionally gave positive results. Rare giant cells, usually of foreign body type and containing up to twenty nuclei, were seen; they occurred more fre-

Fig. 10 (case 3).—Section of a chronic lesion of the axillary lymph node showing epithelioid cells and hyalinization of connective tissue, with amyloid-like tissue at far right (× 110).

quently in the presence of necrosis. Small lymphocytes were usually found scattered among the epithelioid cells. No eosinophils or polymorphonuclear leukocytes were observed, and no endarteritis or perivascular infiltration was noted. In rare giant cells clear vacuoles were seen (fig. 9), and in lesions of long duration fat cells were found around the periphery of the lymph nodes; stains for fat were not used, however.

No fungi were noted with hematoxylin and eosin or bacterial stains. Stains for acid-fast organisms were used on all sections and the results controlled in many cases by checking with slides known to show the bacilli. MacCallum or Brown bacterial stains were used on many sections. No organisms were found with any stain.

Instances which were not recorded as cases of sarcoid in the clinical record library were rediscovered during a review of several hundred microscopic sections from patients whose disease was diagnosed as tuberculosis. The cases of sarcoid often were placed in this classification, even when the diagnosis was suspected clinically and confirmed by biopsy.

TABLE 3.—*Micr*[illegible]*nation*

	Case 1			Case 2	Case 3			Case 4	Case 5	Case 6
Date	8/31/34	12/22/34		6/10/36	12/8/36		9/16/36	3/10/37	5/10/37	[illegible]
Site	Muscle of the arm	Parotid gland	Epitrochlear node	Skin of the arm	Skin of the arm	Epitrochlear node	Axillary node	Deltoid node	Epitrochlear node	[illegible]
Gross examination										
Thick capsule	..	0	0	..	..	0	0	..	..	
Microscopic examination										
Necrosis	0	0	0	0	0	0	0	0	0	
Fibrosis	++	+++	+++	+	++	++	++	+	−	
Tubercles	++	+++	+++	+++	+	++	++	+++	++	
Necrosis	Rare	+	+	0	Rare	0	0	0	Rare	
Giant cells	Rare	+	+	Rare	0	0	Rare	Rare	Rare	
Epithelioid	++++	++++	++++	++++	++++	++++	++++	++++	++++	
Lymphocytes	++	+++	+++	+	+	++	+	++	++	
Eosinophils	0	0	0	0	0	0	0	0	0	
Polymorphonuclears	0	0	0	0	0	0	0	0	0	
Fungi	0	0	0	0	0	0	0	0	0	
Bacteria	..	..	..	..	0	0	..	0	0	
Acid fast	0	0	0	0	0	0	0	0	0	
Original diagnosis										
Clinical	Tuberculosis	Fungus	..	Sarcoid	Sarcoid	..	Sarcoid	Sarcoid	Sarcoid	[illegible]
Pathologic	Tuberculosis	Tubercle reaction	..	Sarcoid	Sarcoid	..	Sarcoid	Sarcoid	Sarcoid	[illegible]

LABORATORY DATA

The laboratory data are presented in table 4. Four patients had a mild hypochromic anemia. The white blood cell count was usually normal or only slightly elevated. I was unable to confirm the impression of some observers that the stab forms are increased, although an increase was noted during intravenous therapy with typhoid vaccine in case 3. In all cases there were eosinophils at some time, and basophils in small numbers were usually present. By making repeated differential counts and by grouping the large lymphocytes and monocytes together, I could confirm the "showers" of large mononuclear cells noted by others. The rise usually appeared to be at the expense of the polymorphonuclear leukocytes. The "showers" could not be correlated with changes in temperature or clinical developments. Abnormal cells were rarely seen.

Of the cases in which the sedimentation rate of the red blood cells was determined, it was increased in those in which the condition was active, and in the 2 cases in which the condition had healed it returned to normal.

The changes in blood chemistry have been discussed in detail in another paper.[4] The serum proteins were above 8 Gm. per hundred cubic centimeters in 8 instances, but the albumin-globulin ratio was reversed in all cases in which the condition was active. In 2 cases in which the condition had healed the total proteins and the abumin-globulin ratio were normal; in 1 instance, however, determinations had not been made during the active stage. Changes in the serum globulin

—Micr ination of the Lesions

	Case 6		Case 7		Case 8	Case 9	Case 10		Case 11	
	6/25/37		6/20/38	10/18/38	8/19/38	11/9/38	4/24/39	4/25/39	4/5/39	
of eck	Lip	Cervical node	Cervical node	Inguinal node	Supraclavicular node	Skin of the abdomen	Inguinal node	Axillary node	Skin of the face	Inguinal node
	..	..	+	0	0	..	..	..	..	..
	0	0	0	±	0	0	0	0	0	0
	++	+	+	+	++	+	+	+	+	+++
	+++	++	++	+++	++	+++	+	0	+++	++
	0	0	Rare	±	+	0	0	0	+	0
	Rare	Rare	Rare	++	Rare	+	0	0	+	Rare
	++++	++++	++++	++++	++++	++++	++	+	++++	++++
	+++	+	++	++	++	+	0	0	+	+
	0	0	0	0	0	0	0	0	0	0
	0	0	0	0	0	0	0	0	0	0
	0	0	0	0	0	0	0	0	0	0
	..	..	..	..	0	..	..	..	..	..
	0	0	0	0	0	0	0	0	0	0
old	..	..	Hodgkin's disease	Sarcoid	Lymphosarcoma	Sarcoid	Tuberculosis	Sarcoid	Sarcoid	Sarcoid
er- sis	..	..	Tuberculosis	Sarcoid	Sarcoid	Sarcoid	Sarcoid	Reticuloendothelial hyperplasia	Sarcoid	Sarcoid

may be of prognostic import. The blood calcium level was increased beyond normal limits in 6 cases and was at the upper limit of normal in 2 others. The calcium tolerance test of London and Bernheim [10] gave peaked, flat and plateau curves. The blood phosphorus was not increased, but the phosphatase was increased at some time in 7 cases in which it was determined and in which the condition was active. The observations could not be correlated with the site or extent of the lesions or with the duration of the disease. A low or normal cholesterol level was observed in 7 cases in which the condition was active. A higher value was obtained in a case in which the condition was active and of short duration and subsequently healed and in a case in which the con-

10. London, I. M., and Bernheim, A. R.: Calcium Tolerance Curves in Paget's Disease of the Bone, J. Lab. & Clin. Med. **23**:18, 1937.

TABLE 4.—*Results of Laboratory Tests*

Case	Date of Admission	Total Protein, Gm. per 100 Cc.	Albumin, Gm. per 100 Cc.	Globulin, Gm. per 100 Cc.	Calcium, Mg. per 100 Cc.	Phosphorus, Mg. per 100 Cc.	Phosphatase, Bodansky Units	Cholesterol, Mg. per 100 Cc.	Bilirubin Tolerance Retention, per Cent	Sedimentation Rate, Mm. per Hour	Hemoglobin, Gm. per 100 Cc.	Red Blood Cells, Millions per Cu. Mm.	White Blood Cells per Cu. Mm.	Polymorphonuclears, per Cent	Stab Cells and Juvenile Forms, per Cent	Eosinophils, per Cent	Basophils, per Cent	Small Lymphocytes, per Cent	Large Lymphocytes, per Cent	Monocytes, per Cent	Bence Jones Protein in Urine	Electrocardiogram
1	8/ 1/34	...	..	...	....	...	...	...	....	..	11.3	....	6,400									
	12/11/34	...	...	...	9.6	3.6	...	240	....	38	14.1	4.48	5,360	75	..	1	1	9	18	3		
	10/14/38	6.2	3.6	2.6	8.6	3.2	5.6	...	....	2	14.5	....	6,920	..	..	..	..	..	..	..	..	Normal
2	6/ 9/36	7.4	2.6	4.8	11.1	3.5	...	...	....	..	12.4	....	.....	..	..	..	..	..	..	..	+	
3	12/ 3/36	7.50	3.17	4.33	9.6	3.7	5.7	133	....	..	11.5	4.90	4,420	63	8	3	0	16	10	0	0	Flat T wave in lead IV
													5,340	57	11	5	2	18	7	0		
	10/28/37	8.2	3.8	4.4	14.2	3.7	...	161	....	50	13.0	5.08	5,680	55	9	4	1	20	5	6		
					13.0	3.0	8.5	...	....	..	....	....	9,040	20	54	3	0	7	4	12		
									....		13.0	5.01	9,920	40	38	0	0	13	3	8		
	9/15/38	8.3	3.1	5.2	14.2	3.0	6.7	...	....	..	....	....	.....	..	..	..	..	..	..	..	0	Prominent P wave in leads II and III
4	3/16/37	...	...	...	....	...	...	...	....	..	13.0	....	10,100	70	8	0	0	20	0	2	..	W QRS in lead IV
		9.3	3.3	6.0	12.8	3.6	...	...	....	..	13.7	5.10	9,840	53	15	3	2	22	5	0	..	Inverted T wave in leads II and III
	8/26/37	...	...	...	....	...	...	...	....	15	13.7	....	7,450									
	9/29/38	9.1	3.3	5.8	10.2	2.5	4.9	...	....	..	....	....	.....	..	..	..	..	..	..	..	0	Diphasic T wave in leads II and IV; inverted T wave in lead III

5	5/ 3/37	...	...	...	....	...	...	...	....	..	13.0	....	5,500	74	8	1	2	6	7	2	
		7.3	...	...	....	...	...	...	....	..	15.9	5.02	8,280	80	0	2	0	5	4	9	
		8.4	3.6	4.8	10.6	3.9	...	...	....	..	....	....	5,600	45	8	3	2	27	7	8	
											17.0	5.70	9,000	80	2	2	0	14	2	0	
	4/27/39	7.0	4.4	2.6	10.8	3.2	3.5	215	....	5	11.9	....	6,150	60	0	3	0	14	9	13	0
6	7/16/37	8.3	3.7	4.6	....	...	...	...	....	..	11.8										
7	5/20/38	...	...	...	....	...	...	...	....	..	....	4.10	6,000	50	9	11	0	23	0	7	
	6/14/38	...	...	...	....	...	...	...	....	..	11.7	4.04	6,750	63	10	8	0	15	0	4	
													4,150	57	4	16	0	15	2	6	
											10.0	4.20	10,080								
	10/17/38	8.5	3.7	4.8	9.1	3.0															
	5/19/39	7.6	3.8	3.8	11.2	3.3	4.4	161	16	24	11.5	....	4,000	57	2	9	2	18	3	9	0
8	8/16/38	...	..	...	14.1	3.7	...	152	....	38	14.0	4.75	9,500	72	..	3	0	16	3	2	..
		6.3	2.4	3.9	14.8	3.6	7.4	...	....	..	....	....	.....	..	..	..	..	..	..	..	+
9	11/ 7/38	9.3	3.4	5.9	9.4	3.7	17.1	...	....	34	13.2	3.79	7,150	72	2	10	0	9	1	6	0
	5/26/39	8.8	2.8	6.0	10.2	3.6	7.3	133	....	43	10.4	....	6,150	55	11	4	0	18	0	12	..
	6/ 1/39	...	...	...	....	3.4	4.9	158	6.2												
10	2/27/39	9.64	...	...	12.6	...	...	...	....	47	15.0	4.96	9,400	39	10	3	0	17	24	7	
		9.6	3.7	5.9	12.6	4.5	7.3	...	....	..	....	....	4,640	53	2	4	0	20	15	6	..
						3.8	6.4	...	....	..	14.9	4.88	6,040	62	1	1	0	24	8	4	
											15.0	5.09	5,860	58	2	2	0	22	13	3	
											15.3	5.05	6,100	60	1	1	0	26	9	3	
	6/ 1/39	...	...	...	....	3.9	6.9	182	28.5	..	....	....	.....	..	..	..	..	..	..	..	0
11	4/ 4/39	8.5	3.0	5.5	9.7	4.1	...	...	....	45	14.3	4.24	5,000	76	2	2	1	10	6	3	..
		7.3	2.1	5.2	10.6	3.1	3.8	...	....	..	13.9	4.40	7,280	70	6	2	2	7	6	7	
						4.1	2.7	...	....	..	....	....	.....								
						4.1	2.7	...	17.4	..	....	....	.....								
	5/26/39	...	...	...	....	3.7	3.0	165	....	32	....	....	9,350	56	16	1	0	9	2	16	0

dition had healed. Definite retention of bilirubin in the bilirubin tolerance test of Soffer [11] was found in the 4 instances in which it was studied. A substance resembling Bence Jones protein in its solubility at the boiling point was found in the urine in 2 cases, in both of which there were suggestive changes in the fingers. It was not present in the cases in which there were definite cysts. The only other urinary abnormality noted was an occasional trace of albumin.

TABLE 5.—Summary of Etiologic S

	Case 1		Case 2	Case 3		Case 4	Case 5	Case 6
Date	12/11/34	10/14/38	6/9/36	12/3/36	9/15/38	3/16/37	5/3/37	4/2
Lymph node								
Culture								
Aerobic	0	..	..	0	0	..	0	
Anaerobic	..	..	..	0	0	..	0	
Sabouraud	0	..	..	0	0	..	0	
Tubercle	0	..	..	..	..	..	0	
Other	..	..	..	..	+	..	..	
Inoculation								
Guinea pig	0	..	..	0	0	..	0	
Rabbit	0	..	..	..	0	..	..	
Mouse	..	..	..	..	0	..	..	
Rat	..	..	..	..	..	..	..	
Chicken	..	..	..	..	0	..	..	
Cutaneous tests								
Positive tuberculin	..	..	..	1:1000 2+	..	1:1000 1+	..	
Negative tuberculin	1:100	1:1000	..	..	..	..	1:100	1:1
Frei	..	..	..	0	..	..	0	
Sarcoid								
1, case 3	..	..	..	+	..	±	+	
2, case 7	..	..	..	..	..	..	..	
3, case 11	..	..	..	..	..	..	..	
Monilia	..	..	..	..	..	..	..	
Blastomyces	..	..	..	..	..	..	0	
Brucella	..	..	..	0	..	..	..	
Blood serum								
Wassermann	0	..	0	0	..	0	0	
Kahn	0	0	0	0	..	0	0	
Monilia	..	0	..	..	0	..	..	
Blastomyces	0	0	..	..	..	..	..	
Other	..	..	..	Tularensis 0	Heterophil 0	..	..	
Sputum								
Smears								
Acid fast	0	..	..	0	0	..	..	
Fungi	Yeast	..	..	0	0	..	..	
Culture								
Bacteria	Friedländer	..	..	Staph. aureus	Staph. aureus	..	..	
Fungi	0	..	..	0	0	..	..	

Neither ova nor parasites were observed in the feces.

Electrocardiographic studies were made in 8 cases, with the finding of prominent P waves in 2 cases and flat or inverted T waves in 2 cases. No cardiac symptoms were observed, though the liver was enlarged in both cases in which the P waves were prominent.

Three grams of ascorbic acid by mouth was required by patient 10, and 2 Gm. by patient 11, to saturate the body, as measured by colorimetric titration of the urine. This amount was in the range of the requirements of normal persons observed in the clinic. The test was repeated in four

11. Soffer, L. J.: Present Day Status of Liver Function Tests, Medicine **14**: 185, 1935.

days on patient 10, and saturation was obtained with the first gram; the amount taken in the amplified diet was sufficient to maintain saturation.

The basal metabolic rate was not elevated in cases 3 and 7.

ETIOLOGIC STUDIES

Cutaneous tests with tuberculin were made in all but 2 cases, starting with dilutions of 1 : 100,000 and gradually increasing the dose. The Frei

...iologic Studies

...se 6	Case 7			Case 8	Case 9		Case 10		Case 11	
...26/37	6/14/38	10/17/38	5/19/39	8/16/38	11/7/38	5/26/39	2/27/39	4/3/39	4/4/39	5/26/39
..	..	+	..	..	..	..	..	..	..	0
..	..	0	..	..	..	..	..	..	..	0
..	..	0	..	..	..	..	..	..	..	0
..	..	0	..	..	..	..	..	..	..	..
..	..	0	..	..	..	..	..	..	..	0
..	..	0	..	..	..	..	..	..	..	0
..	..	..	..	..	..	..	..	..	..	0
..	..	0	..	..	..	..	..	..	..	0
..	..	0	..	..	..	..	..	..	..	0
..	..	0	..	..	..	..	..	..	..	0
..	..	..	..	..	..	..	..	..	10 mg. 4+	..
...	1:1000	..	1:1000	1:100	1:1000	..	..	1:100	1:10	..
..	..	..	0	0	2+	0	..	0	0	..
..	..	..	..	..	..	..	..	..	..	..
..	..	..	±	..	0	..	..	0	0	..
..	..	..	0	..	..	0	..	0	..	+
..	..	..	1+	0	..	0	0	±	0	..
..	..	..	0	..	..	0	0	0	0	..
..	..	..	1+	..	±	..	..	..	..	..
0	0	..	..	0	3+ 0 0	..	..	0	0	..
0	0	..	..	0	3+ 0 0 1+	3+	1+	0	0	..
..	..	..	0	..	..	0	..	0	0	0
..	..	..	0	..	..	0	..	0	A-C	0
..	..	..	..	Brucella 0 Tularensis 0 Typhoid 1:320	..	..	..	..	..	..
..	..	..	..	..	..	..	0	0	0	0
..	..	..	..	..	..	..	0	0	0	0
..	..	..	..	Staph. aureus	..	..	Staph. aureus	..	..	..
..	..	..	..	..	..	..	0	0	0	..

reaction was faintly positive for twenty-four hours in case 9, but it was negative five months later. Cutaneous tests with blastomyces filtrate 1 : 3 and with undiluted stock Monilia albicans vaccine were done; faintly positive reactions were occasionally observed in tests repeated later. An extract from a lymph node of patient 3, prepared according to the method of Williams and Nickerson,[6] gave questionably positive reactions when injected into the skin of 3 patients, with absolutely negative results in 4 controls, 1 of which had active pulmonary tuberculosis

(tests done by Dr. C. E. Leach, Baltimore, December 1936 to July 1937). Extracts of nodes of patients 7 and 11, similarly prepared, each gave completely negative results in 4 patients, with questionably positive reactions in the patients from whose nodes they were made. It is possible that some variation in the technic of preparation of the second and third antigens was responsible for the different results, for with the short duration of the disease in the second instance it would seem logical that the infecting agent would be present in greater quantity and in a more virulent form than in the first and third specimens from patients in whom the disease was chronic.

Agglutination by the blood serum of M. albicans and complement fixation with blastomyces antigen were absent in 7 cases. Only patient 10, with a positive history of treated syphilis, and patient 9, with no history of syphilis, gave occasional positive serologic reactions for syphilis.

Examination of the sputum, when obtainable, gastric contents, nasal scrapings and urine in some cases failed to reveal acid-fast organisms. An unidentified budding fungus was seen in fresh unstained preparations once in the sputum of patient 1, but further search was futile. Direct smears of the removed lymph nodes in this case likewise gave negative results. Cultures of sputum for fungi were made in 4 cases, with uniformly negative results.

Specimens of excised lymph nodes were planted aerobically and anaerobically on blood agar at 37 C., on Sabouraud's medium at room temperature and occasionally on acid-fast mediums. In 3 instances cultures were planted on plain agar over benzene and petrolatum for soil bacteria. In case 3 a single yellow colony of pleomorphic gram-positive bacilli, some of which were partially acid-fast, was recovered, but the organism died out on subcultures before it could be identified. The colony and smears resembled in some respects the organism recovered from a patient with a condition resembling sarcoid by Mellon and Beinhauer.[12] In patient 7 a small gram-negative coccobacillus was recovered but likewise died out before it was identified.

Inoculations of excised nodes gave uniformly negative results in guinea pigs, rabbits, chickens, mice and rats. With the exception of rabbits and chickens duplicate animals were inoculated. In the guinea pigs tuberculin tests were done on all and brucellergin tests on some before the animals were killed. No gross lesions were observed in any; occasional microscopic sections were made. I did not attempt to repeat the work of Schaumann, who reinjected the ground-up lymphoid material of the first into succeeding series of animals.

12. Mellon, R. R., and Beinhauer, L. G.: The Pathogenesis of Noncaseating Tuberculosis of the Skin and Lymph Glands, Arch. Dermat. & Syph. **36**:515 (Sept.) 1937.

TREATMENT

Treatment has been empiric. All the patients were advised to take a high calory, high vitamin diet, with cod liver oil and tomato or orange juice, to rest and to remain in the sunshine as much as possible. Three patients received ultraviolet irradiation, eight to ten exposures, which was gradually increased to eight minutes' duration, but there was no permanent improvement. One patient had received ultraviolet irradiation in another hospital without benefit. Roentgen ray therapy has been tried in 1 case, but sufficient time has not elapsed to evaluate it. Hyperpyrexia, induced by the intravenous administration of typhoid flagella antigen, caused no improvement in 1 case. Sodium gold thiosulfate given intravenously has been used sporadically with no noticeable benefit.

Intravenous injection of neoarsphenamine was credited by patient 5 with causing improvement. Other patients had received the drug before they were seen or have since received it in treatment of syphilis, with no benefit. Desensitization to Williams and Nickerson's antigen might be tried in patients who react positively on cutaneous test to it.

Iodides have been given without harm to 1 patient with lesions in the lungs. Several other patients who have similar roentgen appearances and similar chemical changes in the blood but have not had biopsies done and hence are not included in the series have been given iodides with no harm or benefit. The sputum was uniformly increased under iodides but remained negative for acid-fast organisms and fungi.

The recovery of Snapper's [8] patient 3 coincided with the administration of ascorbic acid. The maintenance of the blood of the patients near saturation caused no immediate improvement.

COMMENT

The disease may be confused clinically with tuberculosis, Hodgkin's disease, lymphosarcoma, leukemia and fungous infections; the correct diagnosis is usually reached by exclusion. The condition in Negroes may run a short course, with marked lesions during the active stage, but completely clear up. The extent of the weight loss in the patients of this series is greater than would be expected from the experience of others. The occurrence of lesions in striated muscle, and in the tibia, ulna and ribs is uncommon. The unusual distribution of the enlarged lymph nodes and the involvement of the nares and eyelids tend to differentiate this disease from others. The chronicity and the low mortality rate indicate an etiologic agent of low virulence.

The sedimentation rate of the red blood cells cannot be used as an indicator of the activity of the disease process, for hyperglobulinemia increases the rate.[13] The lymphocyte-monocyte ratio cannot be used for

13. Jeghers, H., and Selesnick, S.: Hyperproteinemia: Its Significance, Internat. Clin. **3**:248, 1937.

prognosis, as in tuberculosis. The definite tendency toward neutropenia and leukopenia are consistent with (1) the observations on the blood in virus diseases, such as measles and the common cold (the absence of a demonstrable etiologic agent may point toward a virus as the cause of the disease) and (2) the absence of an allergic state (anergic phase) if the disease is tuberculous in origin. The constant observing of eosinophils in the blood, on the other hand, points toward an allergic state.

The chemical studies of the blood indicate no relation of the osseous lesions to hyperfunction of the parathyroid glands. The changes in the serum proteins may indicate activity in the lesions. From the similarity of the fractional precipitation curves of blood serum in these patients to those in patients with disease of the liver,[14] the evidence of diminished excretory power of the liver, as shown by bilirubin tolerance tests, and the invasion and fibrosis of the liver observed in patients with sarcoid who came to autopsy,[7] it appears that the liver is damaged to a greater extent than is usually recognized. The fractional precipitation curves of blood serum and the observing of substances resembling Bence Jones protein in the urine may indicate the formation of abnormal proteins.

The etiologic studies have elicited no new positive data. The use of rabbits, mice, rats and chickens, in addition to the usual guinea pigs, should make possible the recovery of atypical tubercle bacilli. The occasional faintly positive reactions of the skin to the tests with fungi are observed in many healthy persons. The failure to duplicate the results of Williams and Nickerson with cutaneous tests to an extract of tissue may be due to the use of lymph node in place of skin. The patient with the most marked cutaneous lesions gave irregularly positive serologic tests for syphilis and could not be used as a source for sarcoid antigen. The ability of the skin of the patients to react is indicated by the immediate appearance of wheal and erythema in response to all antigens exhibited by patients 5 and 7. It is possible that some unrecovered member of the general group of bacteria related to the actinomyces, the leprosy bacillus or the tubercle bacillus is the etiologic agent. The similarity of the bony and facial lesions to those of leprosy has been pointed out by other observers.[15]

The pathologic reaction is not specific for any group of bacteria. Similar epithelioid reactions can be elicited by tubercle bacilli, fungi or

14. Perlzweig, W. A.; Kondritzer, A. A., and Bruch, E.: The Solubility Precipitation Patterns of the Serum Proteins, J. Biol. Chem. **123**:xcii, 1938; unpublished data.

15. Murdock, J. R., and Hutter, H. J.: Leprosy: A Roentgenological Survey, Am. J. Roentgenol. **28**:598, 1932.

even inert substances, such as aluminum hydroxide,[16] lecithin obtained from yeast and phosphatide or wax derivatives of tubercle bacilli[17] or of blastomycetes.[18] Anergic tuberculosis and fungous diseases can be differentiated by cultural methods, animal inoculation and serologic tests. The absence of polymorphonuclear leukocytes and of eosinophils in the tissues would indicate lack of an allergic response. Allergy to fatty fractions of organisms has never been demonstrated in experimental animals; inoculations of lipids leave a residual eosinophilic response at the site.[19] No eosinophils have been present in the tissues of the patients in this series, but other observers have reported them. Necrosis has been more prominent in this series than in others; this phenomenon usually occurs only in the presence of altered tissue reactivity (allergy). Why could not these patients be exhibiting an exaggerated response in the form of epithelioid cells to small amounts of a lipid fraction of a single organism or a variety of organisms, analogous to the necrosis, polymorphonuclear neutrophilic infiltration and edema of the familiar allergic response to proteins? The large mononuclear cell is the one which predominantly responds to lipids. This theory could explain: (1) the absence of positive cutaneous reactions (only protein materials have been used); (2) the failure to recover organisms from the lesions (only a few organisms or breakdown products would be necessary to evoke the response); (3) the occurrence of lesions in lymphoid tissue predominantly, where reticuloendothelial elements are plentiful, and (4) some cutaneous lesions as a reaction to the circulating lipid at a distance from the site of infection (analogous to the "id" reactions of the skin in tuberculosis and fungous diseases). Cutaneous tests to purified phosphatide and other lipid fractions of tubercle bacilli gave negative results in normal animals, with an altered response in tuberculous animals.[19b] Biopsies after injection of minute amounts of lipid into the skin of patients with sarcoid would aid in studying this point. On the basis of present evidence, the conclusion is reached that the etiologic agent is still unknown.

SUMMARY

Eleven patients with generalized sarcoid have been studied over a period of four years, including 2 who have been clinically well for two

16. Olitsky, P. K., and Harford, C. G.: Intranuclear Inclusion Bodies in the Tissue Reactions Produced by Injections of Certain Foreign Substances, Am. J. Path. **13**:729, 1937.

17. Sabin, F. R.; Doan, C. A., and Forkner, C. E.: Studies on Tuberculosis, J. Exper. Med., 1930, supp. 3, pp. 1-152.

18. Baker, R. D.: Unpublished data.

19. (*a*) Sabin, F. R., and Joyner, A. L.: Tubercular Allergy Without Infection, J. Exper. Med. **68**:659, 1938. (*b*) Smithburn, K. C., and Sabin, F. R.: Reactions of Normal and Tuberculous Animals to Tuberculo-Protein and Tuberculo-Phosphatide, ibid. **68**:641, 1938.

years. The group is the second in which Negroes predominate and includes the first American Indian reported.

Definite changes in the content of calcium, protein and phosphatase of the blood were found. The phosphorus and nonprotein nitrogen were not altered. The cholesterol content was usually low or normal in cases in which the condition was active. Bilirubin tolerance tests showed retention. Calcium tolerance tests gave varied results. Substances resembling Bence Jones protein were occasionally present in the urine.

Etiologic studies, with emphasis on fungi and acid-fast bacilli, using animal inoculation, cultures and serologic and cutaneous tests, gave negative results. The cutaneous test suggested by Williams and Nickerson did not give positive results in our patients. The etiologic agent remains unknown.

Hematologic studies have confirmed low or normal white blood cell counts, neutropenia (without a shift to the left in the Schilling hemogram), eosinophilia, monocytosis and increased sedimentation rate. Occasional nonspecific changes were observed in the electrocardiogram.

The pathologic picture varied from that usually reported in the complete absence of eosinophils, the presence of moderate numbers of giant cells in acute lesions and the occasional presence of necrosis and amyloid.

No specific treatment has been discovered.

It is suggested that the reaction may be an exaggerated nonspecific response to a lipid fraction of varied organisms.

REPORT OF CASES

CASE 1.—*Uveoparotid fever for four months; miliary pulmonary involvement; moderate glandular swelling; acute lesions revealed by biopsy; duration two years; patient well for two years.*

J. L., a married Negro farmer aged 26, was observed Aug. 1, 1934, complaining of swelling of the nodes in his neck of four months' duration. The family history was not significant. His wife had given birth to a stillborn child four years previously; a living child was born subsequently. His general health had been excellent except for smallpox at the age of 2 years, frequent epistaxes and frequent attacks of draining ears. Four years previously he had had marked painless swelling of the nodes of the neck for one week.

Four months previously he had noted generalized weakness, dyspnea and enlargement of the nodes of the neck, with remittent fever to 102 F. Painless nodules appeared under the skin over the arms and legs. He had some pain in the chest, and had raised small amounts of sputum in the morning. He had lost 27 pounds (12.2 Kg.). All the joints of the body had been stiff without swelling.

The temperature, pulse and respirations were normal. He was not ill but showed evidence of loss in weight. The skin was clear. All the lymph nodes of the body were enlarged, particularly those at the angle of the right jaw and in the inguinal region. Nodules were felt at the external canthus of the right eye. Paralysis of the sixth nerve on the left side was noted. Other nodules were felt in the muscles of the arms and legs. The tonsils were enlarged. The liver was palpable; the spleen was not felt.

A biopsy specimen of a muscle of the left arm showed epithelioid cells and occasional giant cells. Roentgenograms of the chest showed hilar nodes and small miliary areas in both lungs.

He was placed on a tuberculosis regimen, without improvement. On December 11 he was admitted to the hospital. New complaints included dull headaches, diplopia, polydipsia and polyuria, further loss of weight, 3 pounds (1.4 Kg.), and enlargement of the parotid glands similar to a childhood attack of mumps. The nodules in the muscles had become the size of walnuts. Small ulcers appeared at the corners and on the roof of the mouth and on the arms and legs. The skin itched and the ulcers crusted. The wrists and elbows swelled.

A few crusted papules were noted near the mouth. The skin was dry and scaly. The parotid glands were markedly enlarged, as were all the peripheral lymph nodes; some measured 3 cm. A few dry rales were heard at the angle of the right scapula after coughing. Nodules were felt along the epididymis.

The temperature remained below 38 C. (100.4 F.) except for one rise to 38.4 C. Roentgenograms showed massive soft miliary spread of pulmonary lesions. Roentgenograms of the hands and long bones were normal. On examination of one specimen of sputum yeast cells and filaments were seen. Study of other specimens gave negative results, as did cultures. Biopsies of an epitrochlear node and a parotid gland showed epithelioid cells, with minimal necrosis but no fungi or bacteria. Cultures and inoculations of the nodes gave negative results. All serologic tests for fungi gave negative results.

The patient gained weight resting at home for twelve months. By June 1936, two years after onset, the swelling in the glands and nodes had disappeared; he felt perfectly well and resumed farming. When seen in October 1938, he appeared to be perfectly well. One postauricular node was palpable. Scars were present at the edges of the corneas. The lesion in the chest had entirely cleared except for minimal peribronchial thickening. The tuberculin test and serologic tests for fungi gave negative results.

CASE 2.—*Cutaneous lesions for twelve months; soft infiltration in the middle portion of the lung; decalcification of hands.*

R. P., a farm Negress aged 23, was observed June 9, 1936, complaining of a cutaneous eruption of twelve months' duration. The family history was not significant. She had been married three years; the first pregnancy resulted in a miscarriage, and two others, in children who died by the second day. Her general health was good. She had frequent sore throats in the winter. She contracted gonorrhea in 1935, with vaginal discharge and stiff swollen knees. The Wassermann reaction had been positive in January 1936, and she had received intravenous therapy twice weekly since.

Twelve months before admission she noted the appearance of papules in the skin, first on the eyelids and then on the face, legs and trunk. They were moderately tender to touch, did not itch and never disappeared. Six months previously a slight cough developed, productive of white sputum but not accompanied by fever. She had rare night sweats and nocturia (micturition twice nightly). She had lost 15 pounds (6.8 Kg.).

The temperature, pulse and respirations were normal. She did not appear ill. In the skin were nontender papules without inflammation 5 mm. in size. No lymph nodes were enlarged. The tonsils were large. The liver and spleen were not felt. The lungs were clear on auscultation. Roentgenograms of the lungs showed extensive soft infiltration, chiefly in the middle of the lung fields. Roentgenograms of the hands showed decalcification and early trabeculation. A biopsy of the skin showed typical hard tubercles.

The patient was placed on a tuberculosis regimen, with cod liver oil, milk and sunshine. She reported by letter twenty-seven months later that she was perhaps a little improved.

CASE 3.—*Generalized enlargement of lymph nodes for seven years; progressive involvement of bones; minimal cutaneous and pulmonary changes.*

F. M., a farm Negress aged 27, was first observed Dec. 12, 1936, complaining of pain in the hands and feet which had begun three years before. The family history was not significant. She was single; a pregnancy had ended in a miscarriage at three months. Her general health had been good before the present illness except for pneumonia at the age of 16 and frequent infections of the upper part of the respiratory tract since that time. Constipation with hemorrhoids and occasional periods of bloody diarrhea had been present for ten years. Vaginal discharge had been present for ten years, and the menses were irregular.

Eight years previously the patient had had a sudden onset of pain in the lower part of the abdomen on both sides, which was accentuated by the menses. Seven years previously she had noted gradual painless enlargement of the inguinal nodes. Three years previously aching in the knee joints with swelling and increased heat had begun. The feet, hands, arms and elbows were soon involved. Pain in the hands and feet persisted, and deformity of the phalanges and nails progressed to such a point that she could not use her hands or stand on her feet. Gradual painless involvement of all the nodes of the body ensued. For two years anorexia and nocturia had been present, with some dimness of vision and frontal headache. She had lost 30 pounds (13.6 Kg.) since the onset of the illness, with a loss of 8 pounds (3.6 Kg.) in the preceding two years. Ingestion of a patent medicine ten months previously had been followed by a generalized pustular eruption, most marked on the face, mouth and genitalia.

The temperature, pulse and respirations were normal. The patient appeared chronically ill. The skin was dry and scaling, with a few subcutaneous nodules over the cheeks, arms and legs. All the lymph nodes of the body were enlarged, particularly those along the borders of the pectoral, deltoid and arm muscles; they were rubbery and nontender. The nails of the fingers and toes were thickened and brittle, with longitudinal ridging of some; the terminal phalanges were misshapen. The tonsils were slightly enlarged and ragged. The lungs were clear. The liver and spleen were not felt. A single temperature reading above 38 C. (100.4 F.) was made.

Biopsy of the skin and a lymph node showed hard tubercles with rare giant cells. Roentgenograms of the hands and feet showed extensive trabeculation and cyst formation. Enlarged mediastinal nodes with slight peribronchial thickening were present. On a regimen of ultraviolet therapy in the hospital and exposure to sunshine, rest and ingestion of cod liver oil at home, the patient gained 6 pounds (2.7 Kg.) and felt better than she had in two years. The pain in the joints decreased, and she was doing housework. The skin occasionally itched.

On her next admission, Oct. 28, 1937, the inguinal and axillary nodes had increased in size, and the lacrimal glands were now enlarged. The scleras were clear. The liver was enlarged; the spleen was not felt. The second pulmonic sound was accentuated and split.

She was given twelve daily intravenous injections of typhoid vaccine, resulting in chills and fever. During this time stab forms of the polymorphonuclear leukocytes markedly increased, and the proportion of the various mononuclear cells varied markedly from day to day.

She continued her previous regimen at home and returned to the hospital on Sept. 15, 1938. She had noticed no dyspnea, and the pains in the joints were improved. She was losing weight. The left tibia was sore and swelled intermittently; a cyst was demonstrated at this site by a roentgenogram. Pain was present along the right costal margin, and a slight cough productive of white sputum had developed. The skin showed only scars. The lymph nodes were increasing in size; the axillary nodes were painful. A detached nodule was present at the upper lateral border of the left lobe of the thyroid. Dry rubs without rales were heard over the chest. Roentgenograms of the chest showed no change since the previous examination. The cysts in the feet were increasing in size. A biopsy of a lymph node showed hyalinization of fibrous tissue, complete replacement by epithelioid cells and the presence of amyloid.

CASE 4.—*Marked involvement of the eyes for one year with complete healing in two years; gradual progressive enlargement of the lymph nodes; pulmonary symptoms with no demonstrable lesions in the lungs.*

A. B., an American Indian farmer aged 22, was observed Feb. 15, 1937, complaining of pain in the eyes of one year's duration. One grandfather had died of cancer. He had been married three years; his wife's only pregnancy resulted in a living child. His general health was good. He had frequent earaches, sore throats, epistaxes and nonproductive colds. For three years he had had epigastric pain between meals. He had had jaundice at the age of 6 years.

Twelve months previously infection in the upper part of the respiratory tract had developed, with headache and thick yellow discharge from the left nostril. For six months he had had a slight cough without sputum or fever. One week after onset dimness of vision with slight pain in the eyes began. A small amount of pus had been present for two weeks in one eye. At the onset the inguinal nodes became enlarged and tender, followed by nontender swelling of the other lymph nodes of the body. Soreness in the right hip and left elbow began. For two months anorexia and nausea had been present. He had lost 20 pounds (9.1 Kg.).

The temperature was normal, but tachycardia was present; he did not appear ill. The skin was clear. All the lymph nodes of the body were enlarged up to 1.5 cm. in size, including the preauricular, postauricular, submental and epitrochlear nodes and those near the pectoral and deltoid muscles and on the thigh. The conjunctivas were injected, and iridocyclitis and keratitis were present. The pupils were irregular and fixed. Pain was present over the bridge of the nose, and the septum was scaling but intact. The tonsils were small and slightly injected; the lungs were clear. The spleen was palpable.

Roentgenograms of the hands and feet were normal, and those of the chest showed slight hilar thickening and enlarged glands.

A biopsy of a lymph node near the deltoid muscle showed hard tubercles and no organisms. The lymphoid tissue was entirely replaced by the epithelioid reaction.

He was admitted to the hospital on March 16, 1937. He was afebrile, but the pulse rate remained 100 to 120. He received ultraviolet radiation for ten days and then was sent home to continue treatment with cod liver oil and sun baths. In the course of the next four months the eyes cleared, but he gained no weight and showed no general improvement.

He returned to the hospital on Sept. 26, 1938. He had lost 3 pounds (1.4 Kg.), but was working daily on the farm. The inguinal nodes were sore, and the others were slowly increasing in size. Pain developed under the sternum, with a cough productive of ½ cup of greenish yellow sputum daily, but there was no

fever. Aching was noted in the right hip and knee. He had taken a pint (475 cc.) of cod liver oil weekly for three weeks. A swollen node had developed in his baby's neck, but the child was not available for examination.

The temperature was 38.4 C. (101.1 F.), pulse rate 120 and the respiratory rate 32, but the patient did not appear acutely ill. The nodes were enlarged, rubbery, freely movable and nontender and measured up to 2 by 3 cm. The skin was clear. The eye showed scars only. Moist rales were present in the left midaxillary line. The liver and spleen were not felt.

Roentgenograms of the chest showed enlargement of the hilar nodes with no infiltration of the central portion of the lungs.

CASE 5.—*Painful enlargement of the lymph nodes for two months; duration six months; patient well for two years.*

J. C., a Negro lumber truck driver aged 27, was admitted to the hospital on May 7, 1937, complaining of tender swollen nodes in the neck and groin which had been noticeable for two months. The family history was not significant. He had been married for eight years and had four living children. His general health was excellent. He had had smallpox and malaria in childhood. He had frequent colds and sore throats.

Two months previously the patient had contracted an infection of the upper part of the respiratory tract, which was followed by gradual painful enlargement of the nodes at the angle of the jaw. Generalized enlargement of the lymph nodes soon followed, with moderate pain in the inguinal nodes. Headache was troublesome. He noted some epigastric pain, with occasional nausea and diarrhea. He lost 20 pounds (9.1 Kg.).

The temperature, pulse and respirations were normal. He was not ill. The skin was clear. The lymph nodes were all enlarged, soft or rubbery, discrete and slightly tender. The largest, 6 cm. in size, were in the inguinal region. The epitrochlear nodes measured 3 cm. The popliteal nodes were palpable. The lungs were clear. The liver and spleen were not felt. The tonsils were pale and not enlarged.

Roentgenograms of the hands were normal; the mediastinal nodes were enlarged, but the lungs were clear except for hilar thickening. Biopsies of cervical and epitrochlear lymph nodes showed marked epithelioid reaction, with rare giant cells and minimal necrosis. He was afebrile and was sent home to receive weekly intravenous injections of 0.45 Gm. of neoarsphenamine. After the tenth injection the nodes disappeared, and he felt perfectly well; he received fifteen injections in all.

He returned to the hospital April 27, 1939. He had worked every day since leaving and had gained 20 pounds (9.1 Kg.). For the preceding four weeks he had noted pain below the right scapula and in the axilla, accompanied by slight cough productive in the mornings of small amounts of yellow sputum. The nodes had entirely disappeared except for small submandibular ones. Several pale papules measuring 3 mm. were present on the skin of the face and chest. The cutaneous tests gave markedly positive reactions to all antigens at thirty minutes, with wheal and reticulated erythema, but the reactions all disappeared in twenty-four hours. Roentgenograms of the hands and feet were normal. The mediastinal nodes had disappeared, and only slight peribronchial thickening was present.

CASE 6.—*Generalized enlargement of the lymph nodes for eighteen months; cutaneous lesions; asymptomatic pulmonary involvement.*

J. T., an unmarried Negro yard boy aged 21, was observed June 16, 1937, complaining of a cutaneous eruption of one year's duration. The family history was not

significant. Eighteen months previously small round papules appeared on the penis and the surrounding skin, followed by similar lesions on the buttocks and swelling of the inguinal nodes. One year previously moderately tender lesions appeared around the mouth, nose and back of the neck. The application of salves to the penis was beneficial, but the facial lesions spread. No pus was present. Wassermann reactions were repeatedly negative, and intravenous antisyphilitic therapy caused no improvement.

The temperature, pulse and respirations were normal. Firm smooth papules without inflammation were present on the neck, face and eyelids. Flat circinate irregular lesions were present at the corners of the mouth and on the anterior nares. The cervical, auricular, axillary, inguinal and femoral nodes were enlarged, firm, rubbery, nontender and discrete. The lungs were clear on physical examination.

Biopsies of the skin, the lip and a posterior cervical lymph node showed epithelioid cells, no organisms and scattered brown pigment. Roentgenograms of the chest showed minimal infiltration in the central portion of the lung, peribronchial fibrosis and enlargement of the lymph nodes. Attempts to trace this patient have been futile.

CASE 7.—*Swelling of the lymph nodes for ten weeks; minimal peribronchial thickening; questionable trabeculation of the toes; healing.*

M. P., an unmarried Negro domestic servant aged 27, was admitted to the hospital June 14, 1938, complaining of swelling of the nodes of the neck which had begun ten weeks before. The family history was not significant. Her general health had been excellent. Six months before admission she began to lose weight and to fatigue easily. Ten weeks before admission she noted slowly growing nontender nodules in the neck, under the chin, in the armpits and in the groin. Anorexia had been marked. She had had no fever. The skin had turned noticeably darker, and the hair began to fall out. She lost 25 pounds (11.3 Kg.).

The temperature, pulse and respirations were normal. She was not ill. The skin was clear. The cervical, submental, epitrochlear, axillary, inguinal and pectoral nodes were enlarged, discrete and not tender. The eyes were clear. The tonsils were small. The liver was at the costal margin; the spleen was not felt. The lungs were clear. The temperature remained 38 C. (100.4 F.) or below until a biopsy specimen was taken, when it reached 39.4 C. (102.92 F.) for two days. A cervical node was excised and found adherent to the surrounding tissues. Sections showed hard tubercles, hyalinization of connective tissue and no organisms. The tonsils were removed, but sections were not made of them. Roentgenograms of the chest showed a few hilar nodes.

On a tuberculosis regimen at home the patient gained 9 pounds (4.1 Kg.). Vague pain developed in the lower part of the abdomen. On October 17 an inguinal node measuring 2.5 by 1.5 cm. was excised. The sections showed a similar process to that in the other node. A single colony of a gram-negative coccobacillus was grown on anaerobic blood agar. Roentgenograms of the hands were normal. The hilar nodes were slightly enlarged, and minimal peribronchial thickening was present.

She returned to the hospital May 18, 1939, one year after onset, complaining of pain under the right scapula during the past winter. She had had no fever at home, had gained 16 pounds (7.3 Kg.) and appeared quite well. Some aching had been present in the muscles of the right thigh. The skin and eyes were clear. Postauricular, submaxillary and small cervical, axillary and inguinal nodes were present. On deep inspiration the liver descended 2 fingerbreadths and the spleen 1 fingerbreadth below the costal margin.

Roentgenograms of the toes showed questionable trabeculation. The hilar nodes had receded slightly; the peribronchial thickening was unchanged. Biopsy of another lymph node showed more definite tubercles with more giant cells and slight necrosis. Fat cells were scattered throughout. Cutaneous tests gave immediate reactions to all antigens, with wheals and erythema at thirty minutes, but the reactions disappered in twenty-four hours.

CASE 8.—*Generalized enlargement of the lymph nodes for four months; soft infiltration in the middle of the lungs; questionable cysts of fingers.*

G. B., a white farmer aged 36, was admitted to the hospital Aug. 16, 1938, because of loss of weight for four months. The family history was not significant. He had been married twice, the first wife dying in childbirth. His general health had been good except for an attack of pain in many of the joints accompanied by swelling at the age of 14. He had been examined in the orthopedic clinic in 1935 because of pain in the lower part of the back after an injury. Roentgenograms of the spine had been normal. He had had no enlargement of the lymph nodes or cutaneous nodules at that time but showed signs of mitral stenosis. The liver and spleen were not palpable.

About one year before the patient's admission gradual malaise had begun, followed by the loss of 40 pounds (18.1 Kg.) in the preceding five months. Four months previously he had noted gradual enlargement of all the lymph nodes of the body. One month later a small mass appeared in the epigastrium. He had no fever. The skin did not itch. His libido had decreased. Burning on urination and nocturia had been present for one year.

The temperature, pulse and respirations were normal. He appeared chronically ill. A few nodules were felt in the skin over the back. All the lymph nodes of the body were enlarged, with the largest 4 by 3 cm. in the right supraclavicular fossa. The eyes were clear. The tonsils were slightly enlarged and reddened. The lungs were clear on physical examination. The heart showed no change since the previous examination. The liver was palpable 3 cm. and the spleen 2 cm. below the costal margins. In the right upper quadrant and near the umbilicus were firm nontender masses measuring 5 cm., which were thought to be enlarged intra-abdominal lymph nodes. Large external hemorrhoids were present. The fingers showed rounded tips.

Gastrointestinal roentgenograms were normal. Roentgenograms of the chest showed no enlargement of the mediastinal nodes but soft infiltration in the middle part of the lung fields. Questionable cysts and trabeculation were present in the finger tips. Roentgenograms of the feet were normal. Biopsy of a lymph node showed almost complete replacement of lymphoid tissue by round collections of epithelioid cells, and the intervening connective tissue showed slight hyalinization. Minimal necrosis was present. The patient left before studies were completed and has not been heard from since.

CASE 9.—*Extensive cutaneous lesions for six years; asymptomatic miliary fibrotic lesions of the lungs.*

B. M., a Negro school teacher aged 32, was observed Nov. 7, 1938, complaining of a cutaneous eruption of six years' duration. Several cousins had asthma. She had been married ten years; the only pregnancy resulted in a living child. Her general health had been excellent. She had had smallpox at the age of 9 years.

Six years previously nonitching lesions had appeared on the upper lip and spread to the nose, arms and neck and then to the skin in general, including the genitalia. She received a course of ultraviolet irradiation in 1931 and one hundred intravenous injections of arsenicals in 1933, without improvement.

The temperature and the respirations were normal, and she did not appear ill. Tachycardia (heart rate 100) was present. The skin of the entire body, including the scalp, eyelids, nares, labia and perineum, was covered with raised, nonscaling, linear or circinate lesions. They were not tender or anesthetic. The palms and soles were not involved. A lipoma was present on the left wrist. The nasal septum was intact. No enlarged lymph nodes were felt. The tonsils were atrophied. The lungs were clear on physical examination. The liver and the spleen were not palpable.

Biopsy of the skin of the abdomen showed minimal invasion of the corium and well formed hard tubercles, with rare giant cells and no necrosis. Roentgenograms of the chest showed miliary fine fibrotic areas, with slightly enlarged nodes. Tiny questionable cysts were observed in the fingers.

CASE 10.—*Lesion of left eye for ten years (syphilitic or sarcoid?); enlargement of the lymph nodes for seven years; chronic pulmonary disease without acid-fast organisms or fungi.*

L. B., an unmarried Negro waiter aged 30, was observed Feb. 24, 1939, complaining of a cough of three years' duration. His father had died of diabetes. The patient's general health had been good except that he had had pneumonia at the age of 13. Frequent sore throats were terminated by a tonsillectomy in 1933. He worked as a plasterer's helper for two years.

Ten years previously pain had developed in the patient's left eye. Seven years previously a penile lesion had developed and had been followed by enlargement of the inguinal and postauricular nodes. Syphilitic iritis was diagnosed, and he had received continuous treatment for one year without improvement. An iridectomy had been performed, resulting in complete loss of sight in that eye. Three years before admission progressive shortness of breath had begun, accompanied by a cough productive of yellow sputum, which progressed in one year to the point of incapacitating him for work. He had frequent attacks of pain in the chest, with no fever or hemoptysis. No cutaneous rash or persistent enlargement of the lymph nodes had been present. He had lost 25 pounds (11.3 Kg.) since the onset and 10 pounds (4.5 Kg.) in the past year.

The temperature, pulse and respirations on admission were normal. He did not appear ill. The skin was clear. There was moderate general enlargement of the lymph nodes, including the cervical and epitrochlear nodes. The right pupil was irregular and eccentrically placed, but it reacted to light. The conjunctiva of the left eye was hyperemic; the cornea was opaque, and there was a wedge-shaped scar in the upper portion of the iris. Motion of the left side of the chest was limited, and the percussion note was dull there. Coarse moist rales were present between the scapulas, more marked on the left. The fingers showed slight clubbing. The liver and spleen were not felt.

Biopsy of an inguinal lymph node showed scattered small hard tubercles. Only marked reticuloendothelial hyperplasia was found in an axillary node. The temperature ranged below 37.5 C. (99.5 F.) except for one rise to 38 C. (100.4 F.). Roentgenograms of the chest showed diffuse infiltration of the central portion of both lung fields; the ribs showed suspicious areas of rarefaction. The diaphragm was deformed by adhesions. The mediastinal nodes were slightly enlarged.

CASE 11.—*Marked cutaneous lesions for five years; generalized enlargement of the lymph nodes; massive asymptomatic lesions of the lungs; minimal bone involvement.*

J. F., a Negro tobacco worker aged 30, was seen April 4, 1939, complaining of an eruption on the face which had begun five years before. Two sisters had been

stillborn. His wife had died of a ruptured appendix; one child was living and well. His general health was excellent, although he had frequent infections of the upper part of the respiratory tract.

Five years before admission the patient had noticed several vesicles on his forehead, followed by weeping nontender papules on the bridge of the nose, which had spread to the cheeks, nares and eyelids. The neck, genitalia and perineum were involved three years later. A roentgenogram of the chest taken three weeks before admission, after influenza, showed extensive lesions in the lungs. He had had no fever or cough and had lost no weight. He had received iodides without harm.

The temperature, pulse and respirations were normal, and he was not ill. Over the face was a butterfly distribution of a papular eruption which was also observed on the neck, legs, scrotum, penis and anus. Some areas were crater-like and measured 2 cm. Two ulcers were seen on the roof of the mouth. The cervical, axillary, epitrochlear and femoral nodes were firm, discrete, enlarged and not tender. The tonsils were small and not infected. A few moist rales were present over both lungs. The liver and spleen were not felt. Biopsy of the skin showed tubercles, with occasional giant cells and minimal central necrosis. The epithelium was ulcerated, but no polymorphonuclear reaction was present. The lymph node showed many hard tubercles, with rare giant cells and no necrosis. The connective tissue was markedly hyalinized, and amyloid was present. No organisms were found. Roentgenograms of the fingers and toes showed trabeculation, with a cyst in a cuneiform bone. Roentgenograms of the chest showed extensive fibrosis, chiefly in the middle parts of the lungs, and the diaphragm was markedly deformed. The mediastinal nodes were slightly enlarged.

CRITERIA FOR THE CLASSIFICATION AND DIAGNOSIS OF PERIPHERAL VASCULAR DISEASES

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The study of peripheral vascular diseases has made rapid strides in the past decade, and has now reached the stage at which it can benefit from a clear, concise and descriptive classification. The need for such a classification becomes obvious when an attempt is made to cull the literature or to abstract hospital records. Increasing interest in peripheral vascular diseases has led to rapid accumulation of new knowledge, and the multiplicity of investigative reports has sharpened the need for some degree of uniformity in clinical designation.

Repeatedly, methods of treatment reported to have yielded excellent results are subsequently found to be of no value in other hands. The reason too often is that widely differing stages of a disease process are grouped together as an entity, and cases included in one classification in one clinic are called instances of something else in another clinic.

The simplest and most practical method of classification, we feel, must be one which enforces a complete study of each case reported, which leaves little to conjecture and which is flexible enough to allow still undiscovered factors to be included at a later date. The set of diagnostic criteria here presented is planned for a threefold use: (1) In the individual case it offers a workable means for accurately defining the patient's initial status, (2) it offers a means of determining his progress and (3) uniform diagnostic standards make possible valid comparisons of data from many sources, and permit crystallization of prognostic and therapeutic principles from these data.

Our scheme is patterned after the diagnostic criteria for heart disease published by the Heart Committee of the New York Tuberculosis and

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Health Association.[1] No claim is made that these criteria are ultimate and immutable principles. They are intended as a uniform basis for diagnosis, subject to such modification as time and use may indicate.

A comprehensive diagnosis of peripheral vascular disease should include a statement of: (A) the etiologic agent or agents; (B) the anatomic status; (C) the extent of physiologic impairment, and (D) the functional capacity of the patient.

A. ETIOLOGIC AGENTS IN PERIPHERAL VASCULAR DISEASES

I. Acrocyanosis.—The characteristic signs and symptoms of acrocyanosis [2] may be summarized as follows:

(*a*) The condition occurs predominantly in young women.

(*b*) The involvement is usually bilateral, though it may be unilateral.

(*c*) The usual site of involvement is the fingers, or the hands up to the wrists.

(*d*) Pain is absent.

(*e*) Changes in color do not occur with changes in posture.

(*f*) Exposure to cold produces spasm, low skin temperature and cyanosis of the extremities.

(*g*) Heat or warmth produces rubor and normal skin temperature.

(*h*) The arterial pulsations are normal.

(*i*) Gangrene never occurs.

(*j*) Oscillometric measurement shows normal expansion with arterial pulsation in the involved area.

(*k*) Vasodilatation tests show normal rises in skin temperature.

(*l*) Arteriographic examination shows normal filling of vessels.

(*m*) Microscopic examination of the capillaries during the cyanotic phase may show spasm of the arterioles and dilated venous branches.

The condition may be differentiated from Raynaud's syndrome by the absence of asphyctic changes in color, of pain, even during the cyanotic phase, and of gangrene. It may be distinguished from thromboangiitis obliterans and arteriosclerosis obliterans by the absence of organic changes in both vessels and tissues.

II. Arteriosclerosis Obliterans.—The characteristics of arteriosclerosis obliterans [3] may be noted in the following manner:

(*a*) The disease usually occurs in persons over 50 years of age.

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1. Criteria for the Classification and Diagnosis of Heart Disease, ed. 3, New York Tuberculosis and Health Association, 1932.

2. (*a*) Lewis, T.: Vascular Disorders of the Limbs, New York, The Macmillan Company, 1936. (*b*) Elliot, A. H.; Evans, R. D., and Stone, C. S.: Acrocyanosis: A Study of the Circulatory Fault, Am. Heart J. **11**:431, 1936.

3. Hines, E. A., Jr.: Thrombo-Arteriosclerosis Obliterans, Proc. Staff Meet., Mayo Clin. **13**:694, 1938. Lewis.[2a]

(*b*) The sex ratio in the patients with this disease shows that men predominate over women, 6 to 1.

(*c*) Race is of no significance as an etiologic factor.

(*d*) The lower extremities are the chief site of involvement; in only about 1 per cent of the cases are symptoms noted in the upper extremities.

(*e*) The chief complaint at the onset is usually intermittent claudication. In the later stages, rest pain may occur as a result of either ischemic neuritis or local changes in tissue; also, paresthesias may be noted. Patients may complain of excessive coldness of the limbs.

(*f*) Any degree of tissue degeneration up to ulceration and gangrene may develop.

(*g*) Physical examination usually reveals a cold extremity, flushed when dependent and pallid when elevated, in which there are varying degrees of degeneration of tissue.

(*h*) Pulsations in any or all vessels may be diminished or absent.

(*i*) Oscillometric tracings show diminished to absent pulsations of the limbs.

(*j*) Vasodilatation tests do not produce normal rises in skin temperature.

(*k*) Arteriographic examination shows varying degrees of organic obstruction.

(*l*) Roentgenographic evidence of calcification of vessels is common, but it is not an index of vascular occlusion.

III. Arteriovenous Fistula.—The signs and symptoms of arteriovenous fistula [4] are both local and systemic. The local symptoms may be described as follows:

(*a*) The involvement is most frequently unilateral.

(*b*) The mass of the fistula is usually evident.

(*c*) Bruit and thrill over the mass are continuous.

(*d*) There is high venous pressure in the affected extremity; as a result of this there may occur (1) enlargement of the limb, (2) increased warmth of the limb or (3) recurrent transient edema.

(*e*) Arterial pulsation is diminished below the lesion.

(*f*) Oscillometric readings are high above the lesion and low beneath it.

(*g*) There is increased oxygen tension in the venous return from the limb.

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4. Hitzig, W. M., and Master, A. M.: Arteriovenous Fistula, J. Mt. Sinai Hosp. **1**:269, 1935.

The systemic phenomena depend on many features—for example, the size of the fistula, the caliber of the vessels involved, the duration of the lesion and its distance from the heart, the age and the activity of the patient, and the presence or absence of coexisting cardiovascular disease. The systemic phenomena may be minimal or may include the signs of advanced cardiac failure. The severity of the signs in the following list will vary with the degree of cardiac compensation.

(*a*) The circulation time (arm to tongue) is usually increased, even with normal venous pressure.

(*b*) The venous pressure is unchanged in the compensated phase; in the later stages, when right ventricular failure occurs, it is of course elevated.

(*c*) The systolic arterial pressure is high; the diastolic, low.

(*d*) The pulse rate is elevated. The production of bradycardia on compression of the mass is almost pathognomonic.

Arteriographic examination, when feasible, will usually establish the diagnosis if arteriovenous fistula is present.

IV. Autohemagglutination.—This condition[5] presents vascular symptoms without evidence of vascular pathologic change. A reversible autohemagglutination, which occurs on cooling and disappears on warming, can be demonstrated. In the cooling-agglutination phase, intravascular plugging with the agglutinated cells occurs.

The demonstration of the Donath-Landsteiner phenomenon—that is, autohemolysis—is not necessary, however, for diagnostic purposes. In vitro, agglutination occurs at 10 C. in titers up to 1:1,000, but it does not occur in any concentration at 37 C.

V. Diseases of the Central Nervous System.—All peripheral vascular changes which develop as a result of syringomyelia, poliomyelitis and hemiplegia have this in common: they are essentially changes due to disuse.[6] Loss of function in a limb causes diminished circulation of blood in that limb, in proportion as the demands of muscular activity diminish.[2a] Curtailment of blood supply brings on, in turn, the varying signs of malnutrition of the skin that have been called "trophic changes": coldness and cyanosis of the affected limb, development of atrophy and edema and an excessive susceptibility to cold and physical

5. McCombs, R. P., and McElroy, J. S.: Reversible Autohemagglutination with Peripheral Vascular Symptoms, Arch. Int. Med. **59**:107 (Jan.) 1937.

6. (*a*) Allen, E. V., and Craig, W. M.: Effect of Lesions of the Central Nervous System on the Circulation, Proc. Staff Meet., Mayo Clin. **13**:131, 1938. (*b*) Lewis, T., and Pickering, G. W.: Circulatory Changes in the Fingers in Some Diseases of the Nervous System, Clin. Sc. **2**:149, 1936. (*c*) Kerr, W. J., and Underwood, F. J.: Hemoconstriction of the Vascular System Associated with Cerebral Disease, Am. Heart J. **12**:713, 1936.

trauma, which often result in indolent "trophic" ulcers. In all these states the absence of organic obliterative disease can be confirmed by the fact that eliminating the vasotonic influence of the sympathetic nerve supply results in complete vasodilatation in the limb.

The distinguishing characteristics of these conditions are therefore:

(*a*) Prolonged loss of muscular function in the limb or limbs affected, associated with the history and signs of disease of the central nervous system.

(*b*) Varying degrees of coldness and cyanosis, and changes resulting from nutritional deficiencies, in the affected as compared with the unaffected limbs.

(*c*) Capacity of the vessels in the affected limbs to dilate completely on removal of the sympathetic vasotonic control in those areas.

Brain lesions which involve the vasomotor centers in the region of the hypothalamus occasionally cause vasoconstriction on the side of the body opposite the lesion.[6c] The limbs affected are cold and pale or cold and cyanotic. Pulsations in these limbs are absent or greatly diminished, and there is no vasodilatation in response to measures that abolish sympathetic tone.

Cord tumors that exert pressure on the lateral columns have been known to cause marked peripheral vasoconstriction, the distribution corresponding to the site of the central lesion.

VI. Cervical Rib Syndrome.—The symptoms in this syndrome depend on distortion of the course of the subclavian artery and the distal trunk of the brachial plexus. This distortion may be caused by an anomalous cervical rib or a fibrous band, or by tension at the insertion of the scalenus anticus muscle sufficient to elevate the arch of these structures.[7] In the majority of cases the symptoms are neurologic only; occasionally there is associated vascular involvement. Symptoms usually appear after adolescence.

The neurologic manifestations are:

(*a*) Pain in the deltoid region, shoulder and upper part of the arm. There may be radiation to the back of the neck and head, to the seventh cervical spine or to the ulnar aspect of the hand and arm.

(*b*) Tenderness over the insertion of the scalenus anticus muscle behind the clavicular attachment of the sternomastoid.

(*c*) Relief on inclining the head toward the affected shoulder.

(*d*) Sensory impairment, and later atrophy, along the ulnar side of the hand and forearm (as a result of involvement of nerve fibers originating in the eighth cervical or first dorsal root).

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7. Callander, C. L.: Surgical Anatomy, Philadelphia, W. B. Saunders Company, 1939. Craig, W. M., and Horton, B. T.: Diagnosis and Treatment of Vascular Disorders of the Extremities, S. Clin. North America **18**:899, 1938.

Vascular manifestations:

(*a*) The commonest changes are secondary to pressure on a nerve and are a result of disuse. The limb is colder than its fellow; it may show mild cyanosis and, occasionally, edema. (Stimulation of sympathetic nerve fibers in the brachial plexus, with resulting vasospasm, may be a factor in these changes.) There is no impairment of peripheral pulsation in these cases, and the limb responds normally to vasodilating stimuli.

(*b*) Major vascular changes are rare and are caused by embolism from a thrombus at the site of pressure. The effects vary, depending on the size and location of the embolus, from transient coldness and cyanosis of the digits to gangrene of the finger tips.

Roentgenographic examination will demonstrate an anomalous cervical rib when it is present. More often than not, however, this anomaly is absent, and the diagnosis must rest on clinical recognition of the neurovascular syndrome.

VII. Exposure to Cold.—Apart from its etiologic role in peripheral vascular disease, prolonged intense cold acts as a noxious physical agent on the outlying structures of persons with normal vascular trees, and produces frostbite.

The effect of cold on peripheral vascular tone is twofold: 1. Directly, it brings about vasoconstriction in an exposed limb, and consequent diminution in the volume of blood circulating in that limb. 2. Indirectly, by way of the central nervous system, it causes vasoconstriction of cutaneous vessels, generally in a reflex manner. In normal persons, the sum of these two effects will not ordinarily suffice to arrest completely the circulation to a limb,[2a] but in persons with impaired peripheral vessels this may happen temporarily and reversibly, as in milder forms of Raynaud's disease during the asphyctic phase, or permanently, with resulting tissue death, in more advanced grades of obliterative vascular involvement. An episode of exposure to cold may be the determining factor in the transition from a state of vascular insufficiency still consistent with viability of the tissues to total obliteration of vessels, with development of gangrene.

In some of the so-called functional vascular disorders (acrocyanosis, erythrocyanosis) cold must be classed as the exciting etiologic factor, the predisposing cause being local change in the vessels which renders them excessively sensitive to cold.

VIII. Diabetes Mellitus.—The role of diabetes mellitus in peripheral vascular disease is not that of a direct etiologic agent. Although the disease is not the cause of arteriosclerosis obliterans, it may hasten

the onset of the latter. Thus it has been estimated [9] that pulsation in one or more of the peripheral vessels is absent ten to twenty years earlier in diabetic than in nondiabetic persons. The importance of diabetes mellitus, then, is in modifying adversely the course of the arteriosclerotic process, especially when infection or trauma supervenes.

IX. Embolism and Thrombosis.—Embolism and thrombosis are acute vascular accidents which lead to a dramatic train of tissue change. Differentiation between embolic and thrombotic obstruction of a peripheral artery depends not on the state of the limb affected but rather on associated findings more or less remote from the site of obstruction. The factors to be evaluated are:

(*a*) The presence or absence of a possible source of emboli. The commonest cause is pathologic change in the left side of the heart; the conditions associated with emboli in systemic arteries are mitral stenosis, auricular fibrillation (especially during changes from fibrillation to regular sinus rhythm), congestive heart failure, bacterial endocarditis involving the aortic or mitral valve and coronary thrombosis with infarction of the left ventricle and formation of mural thrombus.

(*b*) The age of the patient. Thrombosis is more commonly the cause of sudden occlusion in old than in young persons. A history of claudication, or other manifestation of previous vascular impairment in the limb also is in favor of the diagnosis of thrombosis rather than embolism.

(*c*) Simultaneous bilateral occlusion is most often embolic in nature, especially if the level of occlusion is below the bifurcation of the aorta. In unilateral occlusions the vascular status in the opposite limb is a diagnostic help, the presence of vascular obliterative disease favoring the possibility of thrombosis.

In a limb which has suffered an occlusive accident, the characteristic vascular change is loss of the pulse distal to the occlusion. Moreover, the insult to the vessel wall at the point of occlusion tends to induce spasm of the vessel for a varying length proximal to the occlusion, as well as spasm of neighboring vessels. The changes in the tissue are the result of sudden profound curtailment of the blood supply, and are an exaggeration of the milder, more gradual ischemia of chronic obliterative disease. These changes vary, in accordance with the degree of impairment of the blood flow. Thus, occlusion of a common iliac artery causes prostrating pain, anesthesia, paralysis, blanching and coldness of the entire limb and rapid development of gangrene, while occlusion below the popliteal artery may cause few or no symptoms

8. Footnote deleted.

9. Olmsted, W. H.: Arteriosclerosis of the Lower Extremities in Diabetes Mellitus, Internat. Clin. **1**:195, 1936.

and may result in nothing more than loss of pulsation in the anterior or posterior tibial artery. The maintenance of viability in the limb depends on:

(*a*) The caliber of the vessel blocked. Other things being equal, the nearer the occlusion is to the aorta the greater the likelihood of gangrene.

(*b*) The presence of adequate collateral circulation. Occlusion of an artery in a young person calls into play expansile healthy collateral vessels, which may reroute enough blood to save the limb. Thrombosis in an elderly patient must be compensated for by collateral vessels, which may themselves be in an advanced stage of obliterative arteriosclerosis.

(*c*) Extension of the clot. Either thrombus or embolus may serve as a nucleus for a propagating thrombus, which may extend for a considerable length in an artery and may occlude the mouths of collateral vessels.

X. Endocrine Dysfunction.—In people passing through periods of endocrine imbalance, such as young girls with menstrual difficulties and women undergoing severe menopausal disorders, vasospastic phenomena may develop. The peripheral vascular manifestations may involve the upper or lower extremities and tend to be symmetric. Numbness, subjective coldness and paresthesias are the commonest complaints. Objectively, the limbs are cold to the touch and may exhibit a cyanotic tinge. But there are neither the episodes of transient asphyctic color changes nor the evidences of impaired tissue nutrition. All the pulses are normally palpable when the limb is warm; there is no pallor on elevation or rubrocyanosis on dependency of the limbs, and there is normal response to vasodilating stimuli.

Psychoneurosis affects the peripheral arterial tree in the same manner as endocrine dysfunction. Here too, the complaints occur predominantly in women, and are results of a sympathicotonia of central origin. The clinical manifestations are those described in the section on endocrine imbalance.

XI. Ergotism.[10]—The incidence of ergotism at present is almost entirely confined to women of fertile age, their histories revealing prolonged use of ergot during the puerperium or for control of uterine bleeding. Recent widespread use of ergot products for the relief of migraine has apparently not been attended by instances of vascular damage. Outstanding findings are as follows:

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10. von Storch, T. J. C.: Complications Following the Use of Ergotamine Tartrate: Their Relation to Treatment of Migraine Headache, J. A. M. A. **111**: 293 (July 23) 1938.

(*a*) The lower limbs are affected earlier and more often than the upper.

(*b*) Impairment is symmetric.

(*c*) The symptoms progress from tingling and cramps to coldness and numbness. There are pallor and marbling of the skin, diminution of peripheral pulsations, subnormal or absent oscillometric readings. In later stages there is inadequate response to vasodilating stimuli.

(*d*) Gangrene, which develops gradually when the disease is severe, is dry and symmetric, and the parts separate by mummification.

(*e*) The systemic blood pressure is frequently elevated.

XII. Erythrocyanosis.[11]—In the differential diagnosis of erythrocyanosis the following points are noted:

(*a*) The disease occurs usually in young and middle-aged women.

(*b*) Uniform or mottled reddish blue discoloration of the skin in the lower half of the legs is characteristic.

(*c*) Involvement is bilateral and does not extend distal to the malleoli.

(*d*) The affected skin feels cold to the touch and dimples on pressure.

(*e*) The circumference of the leg is increased by subcutaneous infiltration of fat, and there may be indurated nodules in the tissue.

(*f*) Arterial pulsation is normal, and the vasodilatation response is normal.

XIII. Erythromelalgia.[12]—The characteristic signs and symptoms of erythromelalgia may be summarized as follows:

(*a*) It is a disorder chiefly of the lower extremities, marked by a paroxysmal throbbing and burning pain in the skin, and accompanied by a dusky mottled redness of the parts.

(*b*) Pain is induced by warmth and dependency and is relieved by cooling and elevation.

(*c*) The skin temperature of the extremity at which distress occurs is constant for the individual patient.

(*d*) Bounding pulses are present; there is no evidence of obliterative arterial disease.

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11. Telford, E. D., and Simmons, H. T.: Erythrocyanosis, Brit. M. J. **1**:629, 1936.

12. (*a*) Smith, L. A., and Allen, E. V.: Erythermalgia (Erythromelalgia) of the Extremities, Am. Heart J. **16**:175, 1938. (*b*) Mufson, I.: Clinical Observations in Erythromelalgia and a Method for Its Symptomatic Relief, ibid. **13**:483, 1937. (*c*) Lowenthal, L. J. A.: Erythromelalgia in East African Native, East African M. J. **11**:397, 1935.

(*e*) Microscopic observation of the capillaries shows that the venules, which appear bright red, are increased in number and enlarged to five times the normal size.

XIV. Phlebitis.—This condition may produce arterial lesions both directly and indirectly.[13] A true periarterial and even arterial inflammation may be set up in the proximity of a phlebitic vessel.[14] Phlebitis may simulate acute arterial occlusion because of spasm of the main arteries of the affected extremity. The spasm is reflex and is mediated through the sympathetic nervous system. The differential diagnosis is based on relaxation of the spasm by vasodilators, chemical, physical, or both.

XV. Polycythemia.[15]—The peripheral vascular findings in polycythemia are:

(*a*) A blue-red discoloration of the skin, observed as deep raspberry red.

(*b*) Increased sensitiveness to cold.

(*c*) Paresthesias of the extremities.

(*d*) Susceptibility to phlebitis, thrombosis and gangrene of the toes.

(*e*) Engorged and distended capillaries.

XVI. Raynaud's Disease and Raynaud's Phenomenon.—The original criteria postulated by Raynaud [16] in 1888 were:

(*a*) Episodes of change in color of the vasospastic type, excited by cold and emotion.

(*b*) Symmetric involvement.

(*c*) Predominance in young women.

(*d*) Normal pulsations in palpable vessels.

(*e*) Absence of extensive gangrene, or its limitation to minimal grades in cutaneous areas.

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13. Homans, J.: Thrombophlebitis in Legs, New England J. Med. **218**:594, 1938.

14. Samuels, S. S.: The Diagnosis and Treatment of Diseases of the Peripheral Arteries, New York, Oxford University Press, 1936. Lewis.[2a]

15. (*a*) Harrop, G. A., Jr.: Polycythemia, Medicine **7**:291, 1928. (*b*) Weber, F. P., and Bode, O. B.: Polycythaemia, Erythrocytosis, and Erythraemia (Vazquez-Osler Syndrome): An Epitome Based on Parkes Weber's Book of 1921 and the Recent Literature of the Subject, London, H. K. Lewis & Company, 1929. (*c*) Norman, I. L., and Allen, E. V.: Vascular Complications of Polycythemia, Am. Heart J. **13**:257, 1937.

16. Raynaud, A. G. M.: On Local Asphyxia and Symmetrical Gangrene of the Extremities, translated by T. Barlow, in Selected Monographs, London, New Sydenham Society, 1888.

To these Allen and Brown [17] have added:

(*f*) Absence of any disease that may be causal.

(*g*) Symptoms of at least two years' duration.

(*h*) Absence of obliterative arterial disease proved by:

(1) Absence of gangrene.

(2) Normal oscillometric readings.

(3) Normal vasodilatation tests.

(*i*) Characteristic changes in the capillary bed at margins of the nails.

True Raynaud's disease is rare (it has been seen once in 4,000 admissions to the Mayo Clinic). More common is Raynaud's phenomenon, which has been defined by Lewis,[2a] Pickering [18] and Hunt [19] as active and intermittent closure of small arteries, the size of the digital arteries, supplying the extremities; the clinical signs are discoloration of the affected parts, which become waxy or fully cyanotic and are often numb, and their fall in temperature to room temperature.

Raynaud's phenomenon [19] may occur in:

(*a*) Normal persons exposed to low temperatures long enough to lower the temperature of the blood.

(*b*) Persons with "hereditary cold fingers."

(*c*) Patients who have had a local injury to the hands or feet, and workers who use vibrating tools.

(*d*) Persons with thromboangiitis obliterans.

(*e*) Persons with arteriosclerosis obliterans.

(*f*) Persons with syphilitic arteritis.

(*g*) Persons with "rheumatic arteritis."

(*h*) Persons with the scalenus anticus syndrome.

(*i*) Persons with advanced pulmonary tuberculosis, leukemia, polycythemia, lupus erythematosus, chronic malaria, chronic arsenical poisoning, osteoporosis or paroxysmal hemoglobinuria.

XVII. Scleroderma.—This disease is usually considered in association with Raynaud's disease, to which it may be a sequel. Two theories are in vogue as to its causation. One holds that intermittent spasm of the digital arteries or those of similar size constitutes the original state, and that this leads to atrophy and fibrosis of the tissues supplied by the vessels. The other is that diffuse scleroderma arises from a primary

17. Allen, E. V., and Brown, G. E.: Raynaud's Disease Affecting Men, Ann. Int. Med. **5**:1384, 1932.

18. Pickering, G. W.: On Clinical Recognition of Structural Disease of Peripheral Vessels, Brit. M. J. **2**:1106, 1933.

19. Hunt, J. H.: The Raynaud Phenomena: A Critical Review, Quart. J. Med. **5**:399, 1936.

disturbance, infectious or toxic, in the skin and subcutaneous tissue, leading to a state of subacute or chronic inflammation, and that fibrous changes in tissue or vessels are secondary to the inflammation.[2a]

This disease affects young women, although it is rare in female children.[20] It is usually preceded by asphyctic color changes in the affected areas. Sclerodactylia is present, but swelling is also present. Necrosis, when it occurs, is superficial. Pigmentation of the affected regions is common, as are arthritic changes both of the atrophic and of the hypertrophic type. The objective signs and tests are those of obliterative arterial disease.

XVIII. Thromboangiitis Obliterans.[21]—This disease may occur in all races and in all climates. Ninety-nine per cent of the patients are males. The age incidence is from 15 to 45 years, but study of pathologic specimens has been strongly suggestive of the possibility of its association, at least, with arteriosclerosis in aged persons. It is recognizably inflammatory and, although its infectious nature is not established, isolated instances of its transmission from patient to operating surgeon have been recorded.[22] Comprehensive statistical studies seem to indicate that although smoking may in many cases aggravate the disease, it in itself does not produce the condition. The disease is chronic, with many acute exacerbations and long periods of remission. In a large proportion of the cases some degree of involvement of the vessels of the upper extremity is present. The veins are not immune; superficial phlebitis is characteristic of the disease. Obliterative vascular phenomena are responsible for the symptoms, of which intermittent claudication is usually the presenting complaint. Pain while at rest may be severe and out of proportion to the evident ischemia; changes in the tissues are common, and, as mentioned before, superficial migrating phlebitis is present in 30 per cent of the patients.

A diagnosis may be made on the basis of the following criteria:

(*a*) Age: young adult, 15 to 45 years old.

(*b*) Sex: male in 99 per cent of the cases.

(*c*) Evidence of obliterative vascular disease—that is, intermittent claudication, pallor, rubor and absence of pulses.

(*d*) Presence of superficial phlebitis.

(*e*) Chronicity.

(*f*) Results of pathologic examination.

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20. Wright, I. S., and Duryee, A. W.: Treatment of Scleroderma with Mecholyl Iontophoresis, Am. Heart J. **14**:603, 1937.

21. Hines, E. A., Jr.: Thrombo-Arteriosclerosis Obliterans: A Clinical Study of Two Hundred and Eighty Cases, Proc. Staff Meet., Mayo Clin. **13**:694, 1938.

22. Allen, E. V., and Lauderdale, T. L.: Accidental Transmission of Thromboangiitis Obliterans from Man to Man, Proc. Staff Meet., Mayo Clin. **11**:641, 1936.

B. ANATOMIC STATUS OF VESSELS AND TISSUES

At first glance, the separation of observations of anatomic status into those concerned with vessels and those concerned with tissue may appear artificial. Consideration, however, will show that such separation is absolutely necessary. Diagnostic efforts in the study of vascular diseases are directed toward an evaluation of the nature of the actual pathologic process present in the vessels and the extent of that process. All the clinical and laboratory tests are designed to give information as to the status of the vessels involved. The changes in the tissue are the end result of the vascular impairment, and help to guide the physician in recognizing progress or lack of progress during or after treatment. Many of these changes are, moreover, due to external causes, such as infection and trauma, which modify the result of the treatment.

For purposes of record, comparison and determination of progress, we have set arbitrary, but sharply defined, criteria for the varying degrees of vascular involvement. In this way only can the statement "Degree of vascular obliteration: 2 plus" have any significance when one examines a patient a year after the original admission, or when one compares cases with those reported elsewhere. Grading of the disease process in the limb as a whole is arrived at after a comprehensive evaluation of the following factors or observations.

1. Vascular Anatomic Status.—Changes in the anatomic status of the blood vessels may be classified as follows:

(*a*) Pallor and rubrocyanosis: Pallor may be demonstrated in a limb with impaired circulation by elevating the limb to an angle of 45 to 60 degrees for two minutes, with the patient supine. Under these conditions, the degree and rate of development of pallor are an index of ischemia in the limb. The effect of gravity may be augmented by having the patient alternately flex and extend the foot at the ankle, the muscular contractions helping to expel the venous blood which might otherwise color the skin. The pallor is usually most striking over the sole. In this test the rapid onset (within a few seconds) of cadaverous pallor is graded 4 plus. Slight pallor at the end of the two minute period is graded 1 plus.

To demonstrate rubrocyanosis, the limb is allowed to hang down, free and relaxed, for a maximum of two minutes. Prompt onset of an intense reddish purple discoloration in the toes or foot is a maximal (4 plus) reaction. Absence of appreciable rubrocyanosis at the end of the two minute period constitutes a normal response and is graded zero.

The conditions for both procedures are an environmental temperature of 25 to 28 C. (77 to 82.4 F.) and a preliminary rest period of at least thirty minutes in the horizontal position.

In this test, what we observe directly is only the status of the cutaneous capillaries and subpapillary venules; only by inference do we estimate the state of circulation in the part. Pallor is the resultant effect of arterial deficiency plus gravity. Rubrocyanosis is caused by the engorgement of dilated venules and capillaries with blood, with marked slowing of the blood flow and excessive deoxygenation.

(*b*) Palpation of pulses: The extremities to be examined should be warm. When the pulsation is but faintly felt it is advisable to take the precaution of checking with the patient's or the examiner's heart rate.

In the lower extremity the pulsation of the dorsalis pedis, anterior tibial, posterior tibial, popliteal and femoral arteries should be searched for. In the upper extremity the pulsations of the radial, ulnar, brachial, and axillary arteries should be examined.

In this examination, minimal grading (0) corresponds to the absence of pulsation of a vessel. From this base, the intensity of pulsation is graded upward from faint (1 plus), to full (4 plus).

(*c*) Temperature of the extremities by palpation: The back of the fingers may be used to evaluate differences in temperature; the results are graded as warm, cool or cold.

(*d*) Oscillometric measurement: This is a mechanical method for measuring the total expansion of a limb, at a given level, with each arterial pulsation. Its value rests chiefly on the fact that it records these pulsations graphically, and thus provides a permanent record for noting progress and for comparison. In our experience, it is not essential for diagnosis, nor may it be uniformly relied on to gage peripheral vascular status. For example, it is by no means rare for a patient to improve clinically and physiologically while showing a simultaneous steady decrease in oscillometric readings.

Under ideal conditions, a recording oscillometer should be used; but it should be understood that standards of normal must be established for each individual oscillometer. These normal readings then correspond to the maximal (4 plus) grade in our scheme, while the absence of pulsation is grade 0. As in the palpation of pulses, basic conditions must be established, including a preliminary rest period, supine posture and sufficient heat to insure fully warm extremities. In cases of impending or actual gangrene or of acute vascular accident, oscillometric observations should not be made, to avoid further trauma from pressure.

(*e*) Roentgenographic examination: Both roentgenography and arteriography have been called on for aid in diagnosis.

(1) Demonstration of calcification in a vessel by roentgenography does not necessarily signify vascular obliterative disease, although it may be used as an index of degenerative change in the vessel wall. The atherosclerotic process which eventually leads to vascular occlusion and

obliteration may for a long time consist only of intimal and subintimal changes, which are not demonstrable by roentgenography.

(*2*) Arteriography, on the other hand, enables one to demonstrate the actual circulatory pattern of a limb. It does not always differentiate spasm from organic obstruction. For a complete description of methods and evaluation of results in arteriography, the reader is referred to special discussions of the subject.[23]

(*f*) Capillary microscopy: The use of capillary microscopy as a means of demonstrating the presence of organic vascular change is still unreliable as a diagnostic procedure.

II. Anatomic Status of Tissues.—Changes in the anatomic status of the tissues may be classified as follows:

(*a*) No changes.

(*b*) Trophic changes without lesions, evidenced by deformed, dry and brittle nails. The skin may be dry and flaky and may show marbling. The veins are collapsed if no varicosities exist. There is absence of hair growth. Muscular atrophy exists, and roentgenologic examination may reveal bony atrophy.

(*c*) Infections, classified as:

1. Dermatophytosis.
2. Cellulitis.
3. Lymphangitis.
4. Phlebitis.
5. Ulceration, (i) superficial or (ii) deep.

(*d*) Gangrene:

1. Following infection.
2. Followed by infection.

(*e*) Loss of members.

C. PHYSIOLOGIC CHANGES

The physiologic changes refer mainly to three factors, intermittent claudication, spasm and vascular reserve.

I. Intermittent Claudication.—The pain of intermittent claudication is exercise pain. This is symptomatic, and its appearance varies with the rapidity and force of muscular contractions. It comes on more readily in cold than in warm weather.

The time it takes for the pain to appear is called claudication time. This can be measured by an ergometer, or simply in terms of the

23. (*a*) Bird, C. E.: The Use in Arteriography of Substitutes for Colloidal Thorium Dioxide, J. A. M. A. **109**:1626 (Nov. 13) 1937. (*b*) Yater, W. M.: Thorotrast Arteriography of the Extremities, Am. Heart J. **12**:383, 1936. (*c*) Allen, E. V.: How Arteries Compensate for Occlusion, Arch. Int. Med. **57**:601 (March) 1936.

distance, in blocks, that a person can walk before the pain sets in. Claudication pain never occurs on rest, and this fact differentiates it from arthritic and neuritic pain. Whatever the physiologic basis for this pain may be, it is evidently the result of an insufficient blood supply to the muscle in activity.

In our clinic we grade claudication time from 0 when the patient can walk unlimited distances without pain to 4 plus, when he cannot walk more than one half of a city block without the onset of pain. Absence of claudication pain does not guarantee adequacy of circulation, as the patient may be prevented from walking by other disease, such as angina pectoris.

II. Spasm.—Spasm of blood vessels is a factor of importance in both the organic and the functional diseases of the peripheral vascular tree. In the so-called functional group, in which no organic involvement is demonstrable, spasm alone is responsible for the clinical manifestations. This group includes acrocyanosis, erythrocyanosis, certain involvements of the central nervous system, anterior poliomyelitis, syringomyelia, some tumors of the brain and spinal cord, vasomotor imbalance of endocrine or psychoneurotic origin and early stages of ergotism and Raynaud's disease.

In the organic vascular diseases, spasm of varying degree is an associated factor. The problem here is to determine how much of the circulatory inadequacy is due to spasm and how much to organic involvement. It is well known that spasm may simulate all the clinical manifestations of acute or chronic obliterative disease. To estimate the presence or absence of spasm we apply the vasodilatation tests described in the following section.

III. Vascular Reserve.—Vascular reserve represents the maximal capacity of a limb for blood circulation. Determination of vascular reserve is the most important single objective in the study of the patient. It is a measure of the degree of vascular involvement, and it is an indication of how much we may hope to attain with suitable therapy. Periodic determination of vascular reserve is useful also as a means of following changes in the vascular status of the patient's limbs.

All tests at present available for the estimation of vascular reserve are based on the capacity for peripheral vasodilatation. In order of physiologic efficiency, the vasodilatation tests are spinal anesthesia, general anesthesia, peripheral nerve block, paravertebral block, the thermal reflex vasodilatation test and intravenous injection of typhoid vaccine. Tests involving estimation of histamine flare, saline wheal absorption, oxygen saturation of the blood, venous filling and intravenous injection of sodium nitrite are not in common use, and are not essential for diag-

nosis. In our clinic we have found the thermal reflex vasodilatation test [24] and the peripheral nerve block [25] both feasible and dependable.

The thermal test has its basis in the fact that when the blood has been warmed peripherally reflex generalized vasodilatation is induced when it reaches the medullary heat-regulating centers, as a mechanism for dissipating the excess heat. This release of vasoconstrictor influence results in increased blood flow to the limbs, and may be estimated by measuring the changes in skin temperature.

The test is performed as follows: After a period of exposure, during which the limbs to be tested reach a constant temperature, the limbs not being tested are immersed in water at 108 to 112 F., and the upper part of the body is wrapped in a blanket. Temperature readings are then taken for thirty minutes from the dorsal aspect of the terminal phalanx of the toes or fingers of the exposed limbs.

The reflex paralysis of vasoconstriction is, of course, incapable of affecting organic narrowing of vessels; incomplete vasodilating response is thus indicative of organic obliterative change in the vessels. When inadequate vasodilatation is observed in the reflex vasodilatation test, the results are checked by the direct method of peripheral nerve block.

This test involves direct blocking of vasoconstrictor impulses to the medium-sized and small arteries. In the upper extremity the ulnar or median nerves are blocked; in the lower extremity the posterior tibial and the common peroneal nerves. A 1 per cent solution of procaine hydrochloride (without epinephrine) is infiltrated about the nerve; the block is then tested by checking the development of anesthesia or paralysis along the area of distribution of the nerve.

In both the reflex vasodilatation and the nerve block tests, the rise of skin temperature to 30.5 C. (86.9 F.) in the toes or to 32 C. (89.6 F.) in the fingers is considered a normal response and is graded 4 plus. Complete failure of the skin temperature to rise above the starting level, even after peripheral block, denotes far advanced impairment of the vascular reserve and is graded 0.

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24. (*a*) Gibbon, J. H., Jr., and Landis, E. M.: Vasodilatation in the Lower Extremities in Response to Immersing the Forearms in Warm Water, J. Clin. Investigation **11**:1019, 1932. (*b*) Landis, E. M., and Gibbon, J. H., Jr.: A Simple Method of Producing Vasodilatation in the Lower Extremities, with Reference to Its Usefulness in Studies of Peripheral Vascular Disease, Arch. Int. Med. **52**:785 (Nov.) 1933. (*c*) Saland, G.; Klein, C., and Zurrow, H.: The Thermal Reflex Vasodilatation Test in Peripheral Vascular Disease, Am. Heart J. **17**:581, 1939.

25. Scott, W. J. M., and Morton, J. J.: Differentiation of Peripheral Arterial Spasm and Occlusion in Ambulatory Patients, J. A. M. A. **97**:1212 (Oct. 24) 1931.

D. FUNCTIONAL CAPACITY OF PATIENT

Patients are grouped in four classes, according to their functional capacity:

Class I: Patients who have organic disease without symptoms.

Class II: Patients who have organic disease (*a*) with minimal symptoms or (*b*) with moderate symptoms.

Class III: Patients who have organic disease and are bedridden because of severe pain at rest, gangrene or infection.

Class IV: Patients who have symptoms without organic disease; "functional" group.

SUMMARY

The classification of a case of peripheral vascular disease may be outlined as follows:

A. Etiologic Agents

B. Anatomic status
   I. Vascular
   II. Tissue

C. Physiologic status
   I. Claudication
   II. Spasm
   III. Vascular reserve

D. Functional status

Progress in Internal Medicine

DISEASES OF THE HEART

A REVIEW OF SIGNIFICANT CONTRIBUTIONS MADE DURING 1939

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WITH THE EDITORIAL ASSISTANCE OF PAUL D. WHITE, M.D.

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A survey of the literature on cardiovascular disease for the year 1939 reveals much that is of interest and importance. The most notable contributions are in regard to congenital heart disease, essential hypertension and the treatment of subacute bacterial endocarditis. Consequently, these subjects have been reviewed in considerable detail.

ELECTROCARDIOGRAPHIC STUDIES

It has long been known that an electrocardiogram similar to that for the adult can be obtained for the embryo at a very early age. With the improvement in amplifying apparatus, electrocardiographic features regarded as characteristic of adults have become recognizable in the electrocardiograms of progressively younger embryos. The studies carried out by Hoff and his associates [1] are interesting in that these investigators were able to secure records from the time that the heart beat of the chick embryo was just commencing through the period of rapid anatomic change leading to the establishment of the fundamental regional divisions of the heart. They found the earliest visible manifestations of cardiac activity in embryos of 29 to 30 hours and obtained the first consistent records when the embryos were 30 to 36 hours old (fifteen somite chick). At this stage the tubular heart is nearly straight and consists almost entirely of ventricle. The electrical record takes the form of a curve which first drops below, then rises above, the isoelectric line. Slightly older embryos (sixteen to seventeen somites) yield records showing a sharp downward deflection, followed by a rapid return to, or above, the baseline, which probably represents the QRS complex. Shortly thereafter the P wave appears, and by the fourth day of development the electrocardiogram has assumed substantially its adult configuration. Thus the authors were able to trace the appearance of all

From the Cardiac Clinic of the Massachusetts General Hospital.

1. Hoff, E. C.; Kramer, T. C.; DuBois, D., and Patten, B. M.: The Development of the Electrocardiogram of the Embryonic Heart, Am. Heart J. **17**:470, 1939.

the major features of the adult electrocardiogram in hearts so young that they lacked completely either a nerve supply or a specialized sinoventricular conduction system.

Ashman and Hidden,[2] as a result of their electrocardiographic studies, have become convinced that the electrical axis of the T wave is of more significance than mere amplitude of the T wave expressed in millimeters. To test this theory, they selected at random several hundred electrocardiograms. Those tracings showing intraventricular block, or inversion of the T waves in lead I were eliminated, as were nearly all those showing inversion of the T waves in lead III. For each remaining electrocardiogram the average QRS axis and the ratio of the height of T_1 to the height of T_3 were determined. This ratio is a convenient way of expressing the electrical axis of the T wave. When their results were plotted on a diagram, it was found that the ratio T_1/T_3 is normally smaller the more the average electrical axis inclines to the right, and vice versa. A line was drawn in the diagram separating the normal from the abnormal T wave axes at different QRS axes. The decision as to whether or not a given T wave axis is abnormal depends on the average electrical axis of the QRS complex. It was found that in heart disease a rightward deviation of the electrical axis of the T wave is a common finding. An exception to the general rule is seen when the S waves are prominent, especially in leads II and III.

A number of authors[3] have continued the study of the chest leads in electrocardiograms. The variations in normal persons are being carefully worked out, and also the abnormalities observed in various

2. Ashman, R., and Hidden, E. H.: Rightward Deviation of the Axis of the T-Wave as an Index of Myocardial Disease, Ann. Int. Med. **12**:1682, 1939.

3. Robinson, R. W.; Contratto, A. W., and Levine, S. A.: The Precordial Lead: I. Findings for Patients with Normal Hearts and Those with Heart Disease Other Than Myocardial Infarction, Arch. Int. Med. **63**:711 (April) 1939. Contratto, A. W.; Robinson, R. W., and Levine, S. A.: The Precordial Lead: II. Findings for Patients with Myocardial Infarction, ibid. **63**:732 (April) 1939. Vander Veer, J. B., and Edwards, J. C.: The Significance of Small and Absent Initial Positive Deflections in the Chest Lead, Am. J. M. Sc. **197**:663, 1939. Stewart, H. J., and Bailey, R. L.: The Effect of Posture on the Form of Precordial Leads of the Electrocardiogram, Am. Heart J. **18**:271, 1939. Geiger, A. J.: A Comparative Study of Precordial Leads IV R and IV F, ibid. **18**:715, 1939. Wood, P., and Selzer, A.: Chest Leads in Clinical Electrocardiography, Brit. Heart J. **1**:49, 1939. Kossmann, C. E., and de la Chapelle, C. E.: The Precordial Electrocardiogram in Myocardial Infarction: II. Observations on Cases of Infarction of the Posterior Wall of the Left Ventricle, Am. Heart J. **18**:344, 1939; III. Observations on Cases in Which the Lesions Were Diffuse, ibid. **18**:352, 1939. Mortensen, V.: Analysis of the QRS Complex in Precordial Leads in Cases of Anterior Wall Infarction, Nord. med. (Hospitalstid.) **3**:2749, 1939. Evans, C.: Changes in the Chest Lead Electrocardiogram in Coronary Thrombosis, Brit. Heart J. **1**:161, 1939.

types of heart disease and in other disease states. In general, the findings are similar to those previously reviewed.[4]

Only a few years ago inversion or marked lowering of the T waves in leads I or II of the electrocardiogram was nearly always regarded as evidence of coronary heart disease. Gradually there has accumulated a list of exceptions to this rule, which has now reached such proportions that there is danger of underestimating its significance. Barker and his associates [5] have shown that marked lowering of the T waves may occur as a result of overventilation (alkalosis) and that acidosis is accompanied by an increase in the amplitude of T. Thomson [6] studied the effect of postassium salts on the form of the electrocardiogram and found that in general the administration of potassium salts was followed by an increase in the height of the T waves. Mainzer and Krause [7] believe that they have found that fear may cause inversion of the T waves and alterations in the form of the ST segments.

ROENTGENOLOGIC STUDIES

Laubry and his associates [8] have published an excellent atlas, beautifully illustrated, on the roentgen examination of the heart and great vessels. This work includes the many important studies made in the authors' clinic over a period of ten years. The teleroentgenography and roentgenokymography of the normal heart and aorta are illustrated in great detail, after which consideration is given to the various etiologic types of heart disease.

There has been continued interest in the determination of heart size by means of the roentgen ray.[9] Of particular interest is the report of

4. Graybiel, A., and White, P. D.: Diseases of the Heart: A Review of Significant Contributions Made During 1937, Arch. Int. Med. **61**:808 (May) 1938; A Review of Significant Contributions Made During 1938, ibid. **63**:980 (May) 1939.

5. Barker, P. S.; Shrader, E. L., and Ronzoni, E.: The Effects of Alkalosis and of Acidosis upon the Human Electrocardiogram, Am. Heart J. **17**:169, 1939.

6. Thomson, W. A. R.: Potassium and the T-Wave of the Electrocardiogram, Lancet **1**:808, 1939; Effect of Potassium on the Heart in Man, Brit. Heart J. **1**: 269, 1939.

7. Mainzer, F., and Krause, M.: Changes of the Electrocardiogram Brought About by Fear, Cardiologia **3**:286, 1939.

8. Laubry, C.; Cottenot, P.; Routier, D., and Heim de Balsac, R.: Radiologie clinique du coeur et des gros vaisseaux, Paris, Masson & Cie, 1939.

9. Jonsell, S.: A Method for the Determination of the Heart Size by Teleroentgenography (A Heart Volume Index), Acta radiol. **20**:325, 1939. Comeau, W. J., and White, P. D.: An Evaluation of Heart Volume Determinations by the Röhrer-Kahlstorf Formula as a Clinical Method of Measuring Heart Size, Am. Heart J. **17**:158, 1939. Hodges, F. J.: Determination of Heart Size, Am. J.

(Footnote continued on next page)

Jonsell, who describes a method of determining heart volume based on the Röhrer-Kahlstorf formula. Teleroentgenograms are taken simultaneously in two directions at right angles, at a predetermined moment of the heart cycle, with the aid of a cathode ray oscillograph. Jonsell also describes a simplification of the method whereby the heart size is more easily determined and without the use of special apparatus.

Robb and Steinberg [10] have added to their previous studies on the visualization of the chambers of the heart and great vessels by means of the radiopaque solution diodrast. Although this method must still be considered as being in an experimental stage, the results are indeed impressive. The value of their procedure is excellently illustrated in the study of a patient with cor pulmonale.

Routier and Heim de Balsac [11] made careful roentgenologic studies of the modifications of the trachea and bronchi associated with various types of heart disease. They review and extend some of their previous observations, showing that the left auricle as it enlarges meets the tracheal bifurcation, into which it penetrates like a wedge. "The two bronchi, being thus forced apart, curve in upon the auricular cap like a rider's legs gripping his horse." This widening of the angle of the tracheal bifurcation may reach nearly 180 degrees (normally 50 to 80 degrees), and the bronchi may be considerably constricted. The authors describe the anatomic relationship between the air passages and the pulmonary arterial tree in normal persons and in patients with various types of heart disease. When the pulmonary arteries are dilated, the bronchi, having to support abnormal weights, are drawn together so that the angle of the tracheal bifurcation becomes more acute. In extreme cases the caliber of the bronchi, especially that of the left, is reduced.

Roentgenol. **42**:1, 1939. Terrill, E. H.: Determination of the Cardiac Area: Simple Substitutes for the Two-Meter Film, the Orthodiagraph, and the Planimeter in Application of the Hodges-Eyster Formulae, ibid. **42**:611, 1939. Ungerleider, H. E., and Clark, C. P.: A Study of the Transverse Diameter of the Heart Silhouette with Prediction Table Based on the Teleoroentgenogram, Am. Heart J. **17**:92, 1939. Kuttner, A. G., and Reyersbach, G.: The Value of Special Radiologic Procedures in Detecting Cardiac Enlargement in Children with Rheumatic Heart Disease, ibid. **18**:213, 1939.

10. Robb, G. P., and Steinberg, I.: Visualization of the Chambers of the Heart, the Pulmonary Circulation, and the Great Blood Vessels in Heart Disease, Am. J. Roentgenol. **42**:14, 1939; Visualization of the Chambers of the Heart and the Thoracic Blood Vessels in Pulmonary Heart Disease: A Case Study, Ann. Int. Med. **13**:12, 1939.

11. Routier, D., and Heim de Balsac, R.: Tracheal and Bronchial Modifications During the Course of Certain Cardiopathies Affecting the Pulmonary Artery, Brit. J. Radiol. **12**:150, 1939.

CONGENITAL HEART DISEASE

Patent Ductus Arteriosus.—The ductus arteriosus is a vascular channel connecting the pulmonary artery and the aorta. In the fetus the blood pumped into the pulmonary artery is shunted through the ductus into the aorta, the lungs being nonfunctioning. At birth the ductus normally closes in the manner so well shown by Barcroft and his associates. Rarely there is a failure of closure and the ductus remains patent throughout life. This is the third most common congenital cardiovascular abnormality. After birth, of course, the flow of blood in the ductus is from the aorta to the pulmonary artery. The added burden thus placed on the heart is directly proportional to the volume of shunted blood. This burden is often sufficient to produce congestive failure and death at an early age. Furthermore, subacute bacterial endarteritis develops as a complication in about one fourth of the cases, with death as a nearly inevitable consequence.

The possibility of ligating or otherwise obliterating the patent ductus has long been considered and even attempted, but last year the first successful ligation in man was reported by Gross and Hubbard.[12] The patient was a girl 7½ years of age, who bore the operation very well and who recovered uneventfully in a short time.

Gross [13] describes the operative procedure which he successfully used in 4 cases. An incision is made through the third left intercostal space from the sternum to the midaxillary line, and the rib above is divided at the costochondral junction. Opening the pleural cavity allows the lung to collapse, and an appropriate incision in the pleural covering of the mediastinum leads directly to the ductus arteriosus. The diameter of the ductus has little bearing on the possibility of ligating it, but the length is important; if the length is 0.5 cm. or more, it can be easily ligated.

Hubbard and his associates [14] have critically evaluated the indications for surgical ligation of a patent ductus arteriosus. It is their opinion that retardation of growth, peripheral signs of an arteriovenous shunt of considerable magnitude or evidence of cardiac insufficiency are the important indications for operation. They rightly point out that while ligation of a patent ductus may lessen or remove the danger of

12. Gross, R. E., and Hubbard, J. P.: Surgical Ligation of a Patent Ductus Arteriosus: Report of First Successful Case, J. A. M. A. **112**:729 (Feb. 25) 1939.

13. Gross, R. E.: A Surgical Approach for Ligation of a Patent Ductus Arteriosus, New England J. Med. **220**:510, 1939.

14. Hubbard, J. P.; Emerson, P. W., and Green, H.: Indications for the Surgical Ligation of a Patent Ductus Arteriosus, New England J. Med. **221**:481, 1939.

subacute bacterial endarteritis, there is no definite proof of this. The optimum age for operation would seem to be in childhood before the second decade, when the incidence of subacute bacterial endarteritis increases, and after the period of infancy.

Congenital "Aneurysmal" Dilatation of the Left Auricle.—Semans and Taussig [15] describe an enormous saccular dilatation of the left auricle in a 5 year old child. It is thought to have been due to a congenital abnormality either in the blood supply of the affected area or in the auricular myocardium. The authors reviewed the pertinent literature but were unable to find any record of a saccular dilatation of the left auricle that was believed to have been due to a congenital abnormality.

RHEUMATIC HEART DISEASE

Causes.—The etiologic factors of rheumatic fever remain unknown. A preliminary report [16] describing a pleuropneumonia-like organism obtained from rheumatic exudates has not been substantiated.

Eagles and Bradley,[17] in their latest report, present good evidence that a specific virus is not present in the lesions of rheumatic fever. They were unable to confirm the observation that rheumatic exudates yield "elementary bodies" on centrifugation which are specifically agglutinated by the serum of patients with active rheumatic fever. They obtained just as many positive agglutinations with serum from patients with nonrheumatic arthritis as with serum from patients with rheumatic fever. Furthermore, in cases of rheumatic fever there was not found to be any relationship between the positive agglutination test and the clinical activity of the disease.

Coburn and Pauli [18] have demonstrated secondary antigens and antibodies in patients with rheumatic fever. Reference should be made to the original article for the details of their theory and experiments.

Laboratory Tests.—One of the most difficult and important problems arising from the treatment of patients with rheumatic heart disease is that of determining whether or not active rheumatic infection is present. Much help is derived, in the solution of this problem, from a study of the white blood cells and a determination of the red blood cell sedimentation rate. More accurate standards than have heretofore been avail-

15. Semans, J. H., and Taussig, H. B.: Congenital "Aneurysmal" Dilatation of the Left Auricle, Bull. Johns Hopkins Hosp. **63**:404, 1938.

16. Swift, H. F., and Brown, T. M.: Pathogenic Pleuropneumonia-like Microorganisms from Acute Rheumatic Exudates and Tissues, Science **89**:271, 1939.

17. Eagles, G. H., and Bradley, W. H.: The Agglutination of Suspensions of Virus-like Particles Prepared from Exudates in Acute Rheumatic Fever, Quart. J. Med. **8**:173, 1939.

18. Coburn, A. F., and Pauli, R. H.: Precipitinogen in Serum Prior to Onset of Acute Rheumatism, J. Exper. Med. **69**:143, 1939.

able have been published by Osgood and his corps of workers.[19] They determined the total, differential and absolute leukocyte counts and sedimentation rates of healthy persons in four age groups, namely, 4 to 7, 8 to 14, 15 to 18, and 19 and over. They did not find within the groups any significant age or sex difference in the total, differential or absolute leukocyte counts or in the sedimentation rates. The group differences in regard to the white blood cells are given in detail. In regard to the sedimentation rate, the findings were generally the same for each group. The greatest number of determinations fell in the lower ranges, and a rate of 15 mm. in forty-five minutes represented the upper limit of normal values; it included 80 per cent of the results. Higher values, they believe, were due to chronic infection in the tonsils, teeth or sinuses not detectable in the routine physical examination.

Schultz and Rose[20] studied the "formol gel" reaction in the blood of patients with rheumatic fever, and their results suggest that this test may be a valuable aid in the diagnosis of active rheumatic carditis. The test consists in adding 2 drops of a 40 per cent solution of formaldehyde to 1 cc. of the serum to be tested. With normal serum no obvious change occurs, but with pathologic serum an opaque gel forms. This gel formation is invariably associated with hyperglobulinemia, although other factors may be important. It is interesting that the increased sedimentation rate of red blood cells has a similar association. Schultz and Rose found that in various febrile illnesses of nonrheumatic origin there was a parallelism between the "formal gel" test and the sedimentation rate but that in children as in adults with rheumatic carditis the results were unique. Early in the course of rheumatic fever negative "formol gel" reactions are frequently associated with very rapid sedimentation rates. With the development of active carditis, positive "formol gel" reactions may appear when the sedimentation rate has actually decreased, and during convalescence the sedimentation rate may drop to very low levels while the "formol gel" reaction remains strongly

19. Osgood, E. E.; Baker, R. L.; Brownlee, I. E.; Osgood, M. W.; Ellis, D. M., and Cohen, W.: Total, Differential and Absolute Leukocyte Counts and Sedimentation Rates of Healthy Adolescents Fifteen to Eighteen Years of Age, J. Lab. & Clin. Med. **24**:905, 1939; Total, Differential and Absolute Leukocyte Counts and Sedimentation Rates of Healthy Children Four to Seven Years of Age, Am. J. Dis. Child. **58**:61 (July) 1939; Total, Differential and Absolute Leukocyte Counts and Sedimentation Rates for Healthy Children: Standards for Children Eight to Fourteen Years of Age, ibid. **58**:282 (Aug.) 1939. Osgood, E. E.; Brownlee, I. E.; Osgood, M. W.; Ellis, D. M., and Cohen, W.: Total Differential and Absolute Leukocyte Counts and Sedimentation Rates Determined for Healthy Persons Nineteen Years of Age and Over, Arch. Int. Med. **64**:105 (July) 1939.

20. Schultz, M. P., and Rose, E. J.: The Formol-Gel Reaction in Rheumatic Fever: An Aid in the Diagnosis of Active Carditis, Pub. Health Rep. **54**:248, 1939.

positive. In other words, the latter test is apparently more specific for active rheumatic carditis.

Clinical Features.—Although the main clinical features of rheumatic heart disease have been known for a long time, many details still await clarification. The natural evolution of a disease with such widespread and diverse manifestations as rheumatic fever can be fully understood only as a result of studying large numbers of patients throughout their lifetime. This will require the work of many investigators over a long period. Additions to the knowledge of the clinical course of rheumatic fever are being made continually, and some day understanding of this disease will be complete. Last year a number of papers [21] appeared dealing with widely varied aspects.

Ritchie, in the St. Cyres Lecture for 1939, brought the discussion of acute rheumatic carditis up to date. He stresses the great individual variations in the response to rheumatic fever and makes the interesting statement that even though the valves remain intact the myocardial lesions may lead to hypertrophy and dilatation of the heart. Jones and Mote have confirmed earlier experience that a close relationship exists between acute infections of the upper respiratory tract and initial or recurrent attacks of rheumatic fever. Bland and Jones find that about 30 per cent of young patients are left without demonstrable damage to the heart after their initial attack of rheumatic fever. In a ten year follow-up study of 314 such patients they found that signs of permanent valvular deformity developed in 25 per cent later on. This delayed appearance of heart disease was associated with recurrent rheumatic fever in two thirds of the group, while in the remaining third it developed insidiously. Massie and Levine studied the prognosis and subsequent developments in acute rheumatic pericarditis. They found that

21. Ritchie, W. T.: Acute Rheumatic Carditis, Lancet **2**:582, 1939. Jones, T. D., and Mote, J. R.: The Clinical Importance of Infection of the Respiratory Tract in Rheumatic Fever, J. A. M. A. **113**:898 (Sept. 2) 1939. Altschule, M. D.: The Relation Between Prolonged P-R Interval and Auricular Fibrillation in Patients with Rheumatic Heart Disease, Am. Heart J. **18**:1, 1939. Gauld, R. L.; Ciocco, A., and Read, F. E. M.: Further Observations on the Occurrence of Rheumatic Manifestations in the Families of Rheumatic Patients, J. Clin. Investigation **18**:213, 1939. Bruetsch, W. L.: Chronic Rheumatic Brain Disease as a Cause of Mental Disorders, Ztschr. f. d. ges. Neurol. u. Psychiat. **166**:4, 1939. Juster, I. R.: The Significance of Rheumatic Activity in Chronic Rheumatic Heart Disease: II. A Method of Classification, Am. Heart J. **17**:669, 1939. Aschoff, L.: Visceral Rheumatism During Childhood, Arch. f. Kinderh. **116**:145, 1939. Bacal, H. L., and Struthers, R. R.: Rheumatic Infection in Childhood: Effect of Surgical Operations on Blood Sedimentation Rate, Canad. M. A. J. **40**:140, 1939. Bland, E. F., and Jones, T. D.: Delayed Appearance of Heart Disease After Rheumatic Fever, J. A. M. A. **113**:1380 (Oct. 7) 1939. Massie, E., and Levine, S. A.: The Prognosis and Subsequent Developments in Acute Rheumatic Pericarditis, ibid. **112**:1219 (April 1) 1939.

although pericarditis is often associated with severe rheumatic infection yet, if the valves are spared, recovery is essentially complete, and the prognosis is good.

Treatment.—We have previously reviewed the results of investigators who have tested the therapeutic value of sulfanilamide in rheumatic fever. It was shown that the drug not only is of no value but actually aggravates the disease. Coburn and Moore [22] have demonstrated further that sulfanilamide when administered to rheumatic subjects after the onset of streptococcic infection of the throat does not prevent rheumatic recrudescences. However, these investigators, as well as Thomas and France,[23a] have found that daily administration of small amounts of sulfanilamide (1 to 3 Gm.) provides almost certain protection against infection by the hemolytic streptococcus and rheumatic activity. Coburn, in a personal communication, urges caution in the use of sulfanilamide, the study still being in the experimental stage.

There have been further reports on the beneficial effect of fever therapy in chorea and in acute rheumatic fever.[23b,c,d] It must be remembered nevertheless that this procedure is still new and that more work needs to be done before it can be generally recommended.

BACTERIAL ENDOCARDITIS

Streptococcus Viridans Endocarditis.—Two excellent reviews appeared in 1939 on endocarditis due to Streptococcus viridans. Middleton and Burke [24] analyzed 88 cases observed at the Wisconsin General Hospital. On the whole, their findings are in accord with present day views regarding this disease. Contrary to the usual teaching, they state that congestive heart failure may sometimes attend or mask this condition. Therapy was uniformly unavailing and included such means as sodium cacodylate, immunotransfusions and the roentgen ray. There was one instance of healed endocarditis.

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22. Coburn, A. F., and Moore, L. V.: The Prophylactic Use of Sulfanilamide in Streptococcal Respiratory Infections, with Especial Reference to Rheumatic Fever, J. Clin. Investigation **18**:147, 1939.

23. (*a*) Thomas, C. B., and France, R.: Preliminary Report of the Prophylactic Use of Sulfanilamide in Patients Susceptible to Rheumatic Fever, Bull. Johns Hopkins Hosp. **64**:67, 1939. (*b*) Bauer, E. L.: Further Studies on the Treatment of Chorea and Rheumatic Infection by Fever Induction, Am. J. M. Sc. **198**:224, 1939. (*c*) Simmons, E. E., and Dunn, F. L.: Fever Therapy in Acute Rheumatic Disease, Arch. Phys. Therapy **20**:547, 1939. (*d*) Ishmael, W. K.: The Use of Autohemotherapy Reinforced with Artificial Fever in Treatment of Rheumatic Disease, J. Oklahoma M. A. **32**:337, 1939.

24. Middleton, W. S., and Burke, M.: Streptococcus Viridans Endocarditis Lenta: A Clinico-Pathologic Analysis of the Experience in the Wisconsin General Hospital, Am. J. M. Sc. **198**:301, 1939.

An article by Capps [25] has been received with unusual interest because of his earlier report of cures following the use of sodium cacodylate. He has studied 139 patients, all followed to the time of death or over a long period of years up to 1937 or 1938. Of the 139 patients, 11 were living from eight to twenty-six years after the attack of endocarditis. These patients with 1 exception were not very ill, and none was suspected of having endocarditis until the appearance of heart murmurs, embolic signs, enlargement of the spleen and positive blood cultures. Curiously enough, all 11 patients were seen prior to 1925, and 7 of the 11, in the years 1923 and 1924, corresponding to the peak incidence of all cases. Capps speculates as to the possibility that the large number of cases observed in the early twenties represented an epidemic in which a milder type of infection was encountered. Or, again, that Str. viridans may go through cycles of changing virulence. He is of the opinion that sodium cacodylate therapy played a minor role and that it is patients with a mild degree of infection who recover.

Recent studies have provided fresh hope for success in the treatment of bacterial endocarditis. This notable achievement has been made possible through the remarkable curative properties of sulfanilamide and sulfapyridine (2-[paraaminobenzenesulfonamido]-pyridine) and the action of heparin in preventing thrombus formation. In bacterial endocarditis the organisms are protected from the natural immune bodies by the accumulating platelet thrombi and debris which form the vegetations on the cardiac valves. The introduction of highly purified heparin, which may be given intravenously, has made it possible to prevent the formation of platelet thrombi in dogs and, it is reasonable to assume, to prevent additional accumulation of platelets in vegetations already formed. This would allow greater opportunity for the chemotherapeutic agents to come into contact with the invading organism. There is another important factor and that is the degree of natural immunity of the host. It has long been believed that the blood of patients with bacterial endocarditis has a high specific antibody titer. Recent observations [26] have shown, however, that this is far from true and that the antibody titer is frequently very low.

Kelson and White [27] report their experience with 7 patients who were treated for Str. viridans endocarditis with sulfapyridine and heparin. From 4 to 6 Gm. of sulfapyridine was given daily before and

25. Capps, J. A.: Subacute Bacterial Endocarditis Due to Streptococcus Viridans with Special Reference to Prognosis, Ann. Int. Med. **13**:280, 1939.

26. Orgain, E. S.: Personal communication to the author.

27. Kelson, S. R., and White, P. D.: A New Method of Treatment of Subacute Bacterial Endocarditis Using Sulfapyridine and Heparin in Combination: Preliminary Report, J. A. M. A. **113**:1700 (Nov. 4) 1939.

during the use of heparin and for one week afterward. Heparin (10,000 units in 500 cc. of saline solution) was administered by continuous intravenous drip (15 to 25 drops a minute) over a period of two weeks. Two patients had reactions to the heparin, and treatment was discontinued, and 2 patients died within a few days. The remaining 3, who were able to take heparin for more than one week, showed striking improvement and were free of all evidence of the disease nineteen, eighteen and four weeks, respectively, after treatment was discontinued. One of these 3, a young man, died of active rheumatic endocarditis several months after treatment for subacute bacterial endocarditis, and at autopsy the lesions of the bacterial endocarditis were found to be healed. The authors stress the fact that this procedure is still in the experimental stage and that it is not to be recommended except under close and careful observation. Recent communications from these workers indicate a high percentage of failures in the further trial of this treatment but with a few patients observed in whom the condition has apparently been controlled by continued administration of sulfapyridine or sulfathiazole (2-[paraaminobenzene]-thiazole). To date it is too early to recognize cures in the patients except in 1, of the first series, who is now perfectly well a year after treatment. One of the patients in the first series who appeared to have been treated successfully suffered a relapse two months after stopping treatment, but his condition is again under control after a second course. There is some question as to the practical value of heparin; certainly the chemotherapy is apparently the most important part of the treatment. There is evidently a great difference in the reaction of different strains of Str. viridans to the drugs, and much further study of this aspect is necessary.

Friedman, Hamburger and Katz [28] report their observations on a patient with subacute bacterial endocarditis who was treated with heparin and who died during treatment as a result of cerebral hemorrhage. Despite the fact that emboli had been given off repeatedly, the cardiac valves, at autopsy, showed only small "clean" vegetations, and there were two necrotic areas on the vegetations, possibly indicating the dissolution of some of the fibrin.

Spink and Crago [29] administered sulfanilamide to 11 patients with Str. viridans endocarditis and to 1 patient with Staphlycoccus albus endocarditis. The last-mentioned patient was apparently cured but died following a relapse seven months later. Only 1 of the others 10 was

28. Friedman, M.; Hamburger, W. W., and Katz, L. N.: Use of Heparin in Subacute Bacterial Endocarditis: A Preliminary Report, J. A. M. A. **113**: 1702 (Nov. 4) 1939.

29. Spink, W. W., and Crago, F. H.: Evaluation of Sulfanilamide in the Treatment of Patients with Subacute Bacterial Endocarditis, Arch. Int. Med. **64**:228 (Aug.) 1939.

definitely improved, and she has remained in good health for nine months. Spink and Crago believe that sulfanilamide and its related compounds will be of doubtful value in the treatment of patients with subacute bacterial endocarditis because of the nature of the focus of infection, the proliferating mass of bacteria beneath the vegetations being too well protected from the action of drugs and antibodies.

Solway and Pritzker [30] report their observations on a patient with endocarditis due to Streptococcus haemolyticus. Spectacular improvement followed the administration of sulfanilamide, but after an interval of five months relapse and death followed.

Gonococcic Endocarditis.—Orgain and Poston [31] describe a case of bacterial endocarditis due to the gonococcus and a nonhemolytic anaerobic streptococcus superimposed on the pulmonary valve. Recovery followed the oral administration of sulfapyridine in moderate-sized doses. Of the two organisms, the gonococcus proved the more vulnerable to chemotherapy, since it disappeared from the blood first. Coincident with the disappearance of the bacteremia, immune bodies appeared, and in a high titer, and the complement fixation test for the gonococcus, initially 4 plus, became negative. The authors believe that these immunologic changes, together with the clinical improvement, are probably indicative of cure.

Futcher and Scott [32] report their experience with sulfanilamide in the treatment of gonococcic endocarditis. Three of the 4 patients treated died; the fourth recovered. The authors point out that although the condition of the patient who recovered from her illness did not completely fulfil the most rigid criteria for establishing the diagnosis, the presence of gonococcic endocarditis seemed very likely.

ARTERIAL HYPERTENSION

Standardization of Blood Pressure Readings.—Sir Thomas Lewis, in his book, "Diseases of the Heart", states that "the fingers should be trained to recognize a high-tension pulse; for a pressure meter can hardly be used as a routine in general practice." This statement has provoked much criticism, for many observers are of the opinion that this method is grossly inaccurate and that every physician should own and

30. Solway, L. J., and Pritzker, H. G.: Sulphanilamide in the Treatment of Bacterial Endocarditis, Canad. M. A. J. **40**:543, 1939.

31. Orgain, E. S., and Poston, M. A.: Gonococcal Endocarditis with Recovery After Sulfapyridine: Report of a Case, New England J. Med. **221**:167, 1939.

32. Futcher, P. H., and Scott, V. C.: Four Cases of Gonococcic Endocarditis Treated with Sulfanilamide, with Recovery of One, Bull. Johns Hopkins Hosp. **65**:377, 1939.

use a sphygmomanometer. The recommendations recently proposed [33] for taking and recording blood pressure certainly represent a point of view different from that of Lewis. While these recommendations are excellent in themselves, it is likely that the general physician will find certain details impracticable. Nevertheless, there is convincing evidence, which will be presented later, that in certain ranges of blood pressure great accuracy is desirable. The chief recommendations are given herewith in abbreviated form.

1. Blood Pressure Equipment: The equipment to be used, whether mercurial or aneroid, should be in good condition and calibrated at yearly intervals for accuracy, and more often if defects are suspected.

2. The Patient: The patient should be comfortably seated, with the arms slightly flexed and the whole forearm supported at the level of the heart on a smooth surface.

3. Position and Method of Application of the Cuff: A standard-sized cuff containing a rubber bag from 12 to 13 cm. in width should be used. A completely deflated cuff should be applied snugly and evenly around the arm with the lower edge about 1 inch (2.5 cm.) above the antecubital space and with the rubber bag applied over the inner aspect of the arm.

4. Significance of Palpatory and Auscultatory Levels: In all cases palpation should be used as a check on auscultatory readings.

5. Position and Method of Application of the Stethoscope: The stethoscope should be placed over the previously palpated brachial artery in the antecubital space, not in contact with the cuff.

6. Determination of the Systolic Pressure: The cuff should be rapidly inflated to a pressure about 30 mm. above the level at which the radial pulse can be palpated. The cuff should then be deflated at a rate of from 2 to 3 mm. of mercury per second. The level at which the first sound regularly appears should be considerd the systolic pressure unless, as already stated, the palpatory level is higher, in which event the palpatory level should be accepted. This should be noted.

7. Determination of the Diastolic Pressure and the Pulse Pressure: With continued deflation of the cuff, the point at which the sounds suddenly become dull and muffled should be known as the diastolic pressure. If there is a difference between that point and the level at which the sounds completely disappear, the American committee recommends that the latter reading should be regarded also as the diastolic pressure. This should then be recorded in the following form: RT (or LT)

33. Standard Method for Taking and Recording Blood Pressure Readings by the Committee for the Standardization of Blood Pressure Readings of the American Heart Association and the Committee for the Standardization of Blood Pressure Readings of the Cardiac Society of Great Britain and Ireland, J. A. M. A. **113**:294 (July 22) 1939.

140/80-70 or 140/70-0. If these two levels are identical, the blood pressure should be recorded as follows: 140/70-70. The cuff should be completely deflated prior to any further determinations.

In our opinion the first two sentences under the last heading do not logically follow each other; that is to say, if the sounds become dull and muffled, they cannot, at the same point, disappear completely. Furthermore, there is little evidence to support the view that the level at which there is complete disappearance of all sounds should also be regarded as the diastolic pressure, but it may be well to note this level.

The committee's explanatory comments and further recommendations are valuable. The necessity of knowing the physical and mental state of the patient at the time the blood pressure is recorded is worthy of emphasis. A corollary of this is the suggestion that when especially careful studies of the blood pressure are to be made, the use of basal blood pressure conditions should be considered. Helpful hints are given in regard to the determination of blood pressure in the presence of cardiac arrhythmias. It should be recognized that the mercury sphygmomanometer, which has often been declared the more accurate instrument for recording blood pressure, may be in error. Too rapid inflation or deflation of the cuff may result in a lag in the rise or fall of the mercury column, with an error even to 20 to 30 mm. of mercury either systolic or diastolic if the stopper at the top of the mercury tube is too tight.

Normal Blood Pressure.—Most physicians are vague in their idea of what constitutes normal arterial blood pressure. This is due in part to the fact that there are physiologic variations in the normal level of blood pressure and in part to the divergent opinions expressed by cardiologists, but, above all, to the fact that a truly comprehensive study of the normal blood pressure range has never been made. The important contribution of Robinson and Brucer [34] has done much to clarify this problem, and their results, startling as they are, must be accepted until disproved.

The report of Robinson and Brucer is based on a statistical study of (1) the blood pressure in 10,883 persons, (2) a study of five to ten year continuous blood pressure records of 500 persons and (3) an appraisal of mortality at various pressure levels.

For the statistical study, 7,478 men and 3,405 women were selected, representing fairly typical portions of all age groups between 20 and 70 years under conditions of general health comparable to those of any

34. Robinson, S. C., and Brucer, M.: Range of Normal Blood Pressure: A Statistical and Clinical Study of 11,383 Persons, Arch. Int. Med. **64**:409 (Sept.) 1939.

random group in the total population. For the men, the mean systolic blood pressure was found to be 121 mm. of mercury (standard deviation of the mean, 17) and the diastolic pressure 74.4 (standrad deviation, 10.5). For the women, the mean systolic pressure was 117 mm. of mercury (standard deviation, 10.8) and the diastolic pressure 71 (standard deviation, 11.5). The authors point out that if one works only with a broad unselected sample it is better to determine where the values congregate than to use averages. Thus the modal blood pressure was 115 mm. systolic and 71 mm. diastolic for the men and 113 mm. systolic and 70 mm. diastolic for the women.

Since the whole group contained both normal and hypertensive persons, Robinson and Brucer rightly concluded that it was not justifiable to draw conclusions concerning normal levels of blood pressure from such a sample. Consequently they arbitrarily excluded all persons with a blood pressure of 140 mm. systolic and 90 mm. or over diastolic; this left a group including 13.3 per cent of the men and 11.5 per cent of the women. Study of this delimited group indicated that men usually have a blood pressure (modal) of 115 mm. systolic and 72 diastolic and women a modal blood pressure of 112 mm. systolic and 70 mm. diastolic.

The next step was the analysis of a group of 500 records continuous over a period of five to ten years. This took into account the variations of blood pressure, which, for the most part, are due to the normal diurnal flux of pressure. They noted that the lower pressures did not show great variation (usually less than 10 mm.) whereas the higher pressures usually varied by 15 to 40 mm. Furthermore, the low pressures (below 120 mm.) almost invariably tended to remain at the same general low level throughout all age groups, while the higher pressures (120 mm. or above) tended to rise to even higher levels with advancing years. Also, it was noted that once a person's pressure shows even intermittent rises into the danger zones of 120 to 130 and 130 to 140 mm., it frequently returns to that level. From these continuous records it was concluded that normal blood pressure should not exceed 120 mm.

The third analysis was made from a consideration of mortality data. The fundamental premise was made that "normal" blood pressure should be consistent with the longest possible life. In other words, what is the vascular tension that leads to the longest life span and what are the levels that shorten life? It was found that mortality increases in direct proportion to increased blood pressure. The important thing is that this holds true not only for the higher pressures (140 mm. and higher) but also for pressures of 120 to 130 mm. There is even some evidence that a pressure of 110 systolic and 70 diastolic is associated with a lower mortality than one of 120 systolic and 80 diastolic.

The general conclusion is drawn that normal blood pressure for men and women is from 90 to 120 mm. of mercury systolic and 60 to 80 mm. diastolic. A normal person attains his mature blood pressure at about adolescence and keeps that range throughout life except for a slight rise at about the twentieth year. Transient elevations of blood pressure should not be ignored, as they often indicate beginning hypertension. Slightly more than 40 per cent of the adult population is either actually or incipiently hypertensive.

Essential Hypertension.—The problem of essential hypertension is still unsolved. Recent studies have not yet revealed the nature of the responsible agent, although progress can be reported. It is by no means an easy matter to evaluate the mass of experimental and clinical data now available. So much work is actively going on along these lines that a review, which is limited to published data, is behind the times.

For a clear statement of the problem the reader is referred to Pickering's article,[35] in which he develops a line of thought rather than an attempt to prove a scientific hypothesis. The subject matter of his review has been previously discussed and need not be considered here.

Causes.—There have been described a number of new methods for the production of permanent hypertension. Page,[37] during the course of experiments designed for another purpose, observed that hypertension developed in animals in which cellophane had been wrapped around the kidneys. Cellophane causes perinephritis, which results in the formation of a fibrocollagenous hull that constricts the renal parenchyma. Similarly, Greenwood, Nassim and Taylor [38] produced permanent hypertension in dogs by applying a collodion cast to one kidney and removing the other. They raise the question as to whether or not the prevention of renal hypertrophy is the provocative factor. It seems that in both sets of experiments the mechanism responsible for the hypertension is similar to that which results from constricting the renal artery by means of the Goldblatt clamp.

Drury,[39] in an excellent study which we failed to review last year, described a unique method for the production of hypertension in rab-

35. Pickering, G. W.: The Problem of High Blood Pressure in Man, Brit. M. J. **1**:1, 1939.

36. Footnote deleted by the author.

37. Page, I. H.: The Production of Persistent Arterial Hypertension by Cellophane Perinephritis, J. A. M. A. **113**:2046 (Dec. 2) 1939; A Method for Producing Persistent Hypertension by Cellophane, Science **89**:273, 1939.

38. Greenwood, W. F.; Nassim, R., and Taylor, N. B.: The Production of Hypertension by the Prevention of Kidney Hypertrophy, Canad. M. A. J. **41**: 443, 1939.

39. Drury, D. R.: The Production by a New Method of Renal Insufficiency and Hypertension in the Rabbit, J. Exper. Med. **68**:693, 1938.

bits. The method consists in placing a ligature loosely around the left renal artery of a baby rabbit and allowing the artery to grow up to the size of the loop. The development of the left kidney is arrested at this stage and remains dwarfed, while the right hypertrophies. Hypertension occurs even in the presence of the hypertrophied right kidney when there is good renal function. After removal of the right kidney the hypertension is increased. Here, again, the underlying mechanism of the production of hypertension is probably the same as in the Goldblatt experiment, but Drury's method offers many advantages.

Goldblatt, Kahn and Hanzal [40] confirmed the work of Rytand in showing that constriction of the aorta just above the level of the renal arteries is followed by hypertension, while constriction just below the level of the renal arteries has no significant effect on the blood pressure above that level.

A number of papers have been published [41] on the nature and action of the renal pressor substance. It is probable that this substance is renin, and it has now been prepared in a highly purified form, a minute amount being sufficient to elevate the blood pressure considerably. Repeated injections result in a diminution of the pressor response, and this is due, according to Page, to loss of "renin-activator" and the development of an "antisubstance."

Clinical Studies.—Weiss and Parker,[42] in a fundamental study on pyelonephritis, showed that this disease in the chronic and in the healed stage should be considered as one type of Bright's disease, for it can lead to kidney failure, severe hypertension and their complications. They studied the natural history of the disease in 100 selected cases and were able to trace the sequence of events from the initial renal lesions to the terminal stage of severe hypertension. They found that hypertension is frequently associated with pyelonephritis and that this association is responsible for 15 to 20 per cent of all cases of malignant

40. Goldblatt, H.; Kahn, J. R., and Hanzal, R. F.: Studies on Experimental Hypertension: IX. The Effect on Blood Pressure of Constriction of the Abdominal Aorta Above and Below the Site of Origin of Both Main Renal Arteries, J. Exper. Med. **69**:649, 1939.

41. Page, I. H.: On the Nature of the Pressor Action of Renin, J. Exper. Med. **70**:521, 1939. Helmer, O., and Page, I. H.: Purification and Some Properties of Renin, J. Biol. Chem. **127**:757, 1939. Williams, J. R.; Diaz, J. T.; Burch, J. C., and Harrison, T. R.: The Relation of the Adrenal Glands to the Action of the Renal Pressor Substance, Am. J. M. Sc. **198**:212, 1939. Swingle, W. W.; Taylor, A. R.; Collings, W. D., and Hays, H. W.: Preparation and Bioassay of Renin, Am. J. Physiol. **127**:768, 1939. Prinzmetal, M.; Friedman, B., and Abramson, D. I.: The Nature of Arterial Hypertension with Special Reference to the Rôle of the Kidney, Ann. Int. Med. **12**:1604, 1939.

42. Weiss, S., and Parker, F., Jr.: Pyelonephritis: Its Relation to Vascular Lesions and to Arterial Hypertension, Medicine **18**:221, 1939.

hypertension. In hypertension accompanying pyelonephritis the symptoms are commonly those of uremia rather than those of severe coronary or cerebral arteriosclerosis; cerebral encephalopathy, neuroretinitis and high cerebrospinal fluid pressure as well as the syndrome of left ventricular failure were frequently observed. It is emphasized that pyelonephritis is the one renal disease which in its incipient stage can be treated effectively.

Among a number of important papers [43] relating to various clinical aspects of hypertension, the monograph by Wagener and Keith on diffuse arteriolar disease with hypertension and the associated retinal lesions is especially noteworthy. They found it possible, from the standpoint of prognosis at least, to divide all cases of essential hypertension into four groups. In the first two the hypertension is relatively benign and the lesion in the retinal arterioles is essentially anatomic, resulting either from previous angiospastic episodes or from long-continued increase in arteriolar tonus without active angiospastic episodes. In the last two groups the hypertension is severe or "malignant," and the essential lesion in the arterioles is active spastic constriction superimposed either on increased arteriolar tonus or on anatomic thickening of the walls of the arterioles or on both.

Hypertension in Eclampsia.—The newer studies on experimental hypertension have offered a plausible explanation for the "toxemias" of pregnancy, the most constant sign of which is arterial hypertension. There is considerable evidence [44] that a humoral factor is involved

43. Wagener, H. P., and Keith, N. M.: Diffuse Arteriolar Disease with Hypertension and the Associated Retinal Lesions, Medicine **18**:317, 1939. Friedman, B., and Prinzmetal, M.: Vasomotor Effects of Blood in Patients with Hypertension and Animals with Experimental Hypertension, Ann. Int. Med. **12**:1617, 1939. Schroeder, H. A., and Steele, J. M.: Studies on "Essential" Hypertension: I. Classification, Arch. Int. Med. **64**:927 (Nov.) 1939. Williams, J. R., Jr., and Harrison, T. R.: Clinical Pictures Associated with Increased Blood Pressure: Study of One Hundred Patients, Ann. Int. Med. **13**:650, 1939. Keith, N. M.; Wagener, H. P., and Barker, N. W.: Some Different Types of Essential Hypertension: Their Course and Prognosis, Am. J. M. Sc. **197**: 332, 1939. de Wesselow, O. L. V. S., and Thomson, W. A. R.: Study of Some Serum Electrolytes in Hypertension, Quart. J. Med. **8**:361, 1939. Rasmussen, H., and Thingstad, R.: Cardiovascular Changes in Essential Hypertension, with Special Reference to Electrocardiogram in Hypertension, Acta med. Scandinav. **101**:237, 1939. Page, I. H.: A Clinical Study of Malignant Hypertension, Ann. Int. Med. **12**:978, 1939. Wilson, C., and Byrom, F. B.: Renal Changes in Malignant Hypertension, Lancet **1**:136, 1939. Mosenthal, H. O., and Lander, H. H.: The Development and Importance of Hypertension in Chronic Bright's Disease, Ann. Int. Med. **12**:1449, 1939.

44. Page, E. W., and Ogden, E.: The Physiology of Hypertension in Eclampsia, Am. J. Obst. & Gynec. **38**:230, 1939. Dieckmann, W. J., and Brown, I.: Do

just as in the hypertension due to renal ischemia. One theory is that chorionic tissue is responsible for this pressor factor and that the stimulus for the production of the latter may be an inadequate supply of blood to the placenta. Another possible explanation, which has some basis in experimental fact, is that pregnancy increases susceptibility to renal ischemia, which in turn may give rise to hypertension.

Treatment.—One of the most dramatic medical announcements that could be made would be that a "cure" has been found for hypertension. More than a hint of this is to be found in the news letter of a recent issue of *Science*. However, the authors themselves [45] are uncertain as to the ultimate value of their method of treatment. And, whereas they can lower the blood pressure of hypertensive animals by oral administration of a kidney extract which does not lower the blood pressure of normal animals, they are uncertain as yet whether such a lowering is desirable or not. Furthermore, they found that in certain instances the animals became quite ill after their blood pressure had fallen and that some of the animals died. Because of this and because the extract is extremely difficult and expensive to prepare in adequate amounts for human use, the clinical experience has been most limited. One or two patients have shown practically no change in blood pressure, possibly owing to inadequate dosage. Several patients have shown what has appeared to be a rather encouraging drop of 20 to 40 mm. of mercury and some simultaneous improvement in their symptoms. Even though these patients were carefully controlled, having been in the hospital for several weeks or longer in most instances, there is still a possibility that the declines observed in them may have been due to a psychic effect or may have been spontaneous. The results in patients may be regarded as encouraging but as not by any means convincing at the present time.

There have been two brief reports [46] on attempted revascularization of the kidney in an effort to lower the blood pressure in patients with hypertension. The theoretic basis for this procedure rests in the fact

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Eclampsia and Preeclampsia Cause Permanent Vascular Renal Pathology? ibid. **37**:762, 1939. Browne, F. J., and Dodds, G. H.: The Remote Prognosis of the Toxemias of Pregnancy, J. Obst. & Gynaec. Brit. Emp. **46**:443, 1939. Dill, L. V.; Isenhour, C. E., and Cadden, J. F.: The Effect of Quantitative Reduction of Renal Blood Flow upon the Pregnant Rabbit, J. Clin. Investigation **18**:641, 1939.

45. Harrison, T. R.: Personal communication to the author.

46. Bruger, M., and Carter, R. F.: Evidence of Communication Between Renal and Omental Blood Vessels Following Nephroomentopexy for Arterial Hypertension in Man: Preliminary Note, Am. J. M. Sc. **197**:832, 1939. Abrami, P.; Iselin, M., and Wallich, R.: Attempt to Treat Arterial Hypertension of Renal Origin by Surgical Vascularization of the Kidney (Nephro-Omentopexy), Presse méd. **47**:137, 1939.

that hypertension produced experimentally by compression of the renal artery may be relieved following the development of collateral circulation. The procedure consists in enveloping the kidney with omentum (nephro-omentopexy). It has been shown by O'Shaughnessy and others that cardio-omentopexy may aid in reestablishing the coronary circulation, and there is every reason to believe that an anastomotic circulation will develop between the kidney and the omentum. However, the two situations are not comparable, and in the case of the kidney it is doubtful if much good can be accomplished.

Except for nephro-omentopexy, there has not been any new development in the surgical treatment of hypertension.[47] Nowak and Walker,[48] largely on theoretic grounds, criticize this form of treatment, and Volini and Flaxman,[49] observing the symptomatic relief and the reduction in blood pressure resulting from nonspecific surgical measures, hold that the relief is comparable to that following resection of the splanchnic nerve.

Observations by Wood and Cash [50] and Short and Johnson [51] confirm previous impressions that blood pressure increases with increase in body weight.

CORONARY HEART DISEASE

Coronary Occlusion and Cardiac Infarction.—In continuation of the excellent series of articles on heparin, Solandt, Nassim and Best [52] describe experiments in which the formation of cardiac mural thrombi in dogs was prevented by injecting heparin intravenously. Their method of regularly producing mural thrombi is of interest. In previous studies

47. Paliard, F., and Etienne-Martin, P.: Surgical Treatment of Malignant Arterial Hypertension: Results and Indications, Presse méd. **47**:893, 1939. Smithwick, R. H.: Surgery of the Sympathetic Nervous System, New England J. Med. **220**:475, 1939. Chabanier, H.; Gaume, P., and Lobo-Onell, C.: Survey Over Results of Interventions Practiced in Forty-Nine Cases of Nephro-Angiosclerosis (Permanent Hypertensive States with Renal Lesions of Arterial Origin), Presse méd. **46**:1818, 1938. Davis, L., and Barker, M. H.: Clinical and Experimental Experiences in Surgical Treatment of Hypertension, Ann. Surg. **110**: 961, 1939.

48. Nowak, S. J. G., and Walker, I. J.: Experimental Studies Concerning the Nature of Hypertension: Their Bearing on Surgical Treatment, New England J. Med. **220**:269, 1939.

49. Volini, I. F., and Flaxman, N.: The Effect of Nonspecific Operations on Essential Hypertension, J. A. M. A. **112**:2126 (May 27) 1939.

50. Wood, J. E., Jr., and Cash, J. R.: Obesity and Hypertension: Clinical and Experimental Observations, Ann. Int. Med. **13**:81, 1939.

51. Short, J. J., and Johnson, H. J.: An Evaluation of the Influence of Overweight on Blood Pressures of Healthy Men: A Study of 3,516 Individuals Applying for Periodic Health Examination, Am. J. M. Sc. **198**:220, 1939.

52. Solandt, D. Y.; Nassim, R., and Best, C. H.: Production and Prevention of Cardiac Mural Thrombosis in Dogs, Lancet **2**:592, 1939.

on coronary occlusion it was found that simply tying the coronary vessels supplying the tip of the left ventricle did not result in the formation of a thrombus in over 100 animals. However, if sodium ricinoleate was injected into the heart muscle just beneath the endocardium, large pendulous thrombi were usually found within half an hour. In a series of animals on which the autopsies were performed one and one-half hours after the injection of the sclerosing solution, macroscopic cardiac mural thrombi were present in every animal, whereas, in comparable experiments, when heparin was administered no macroscopic thrombi were seen, although microscopic clumps of platelets were present in many of the animals. The same results were obtained in two series of animals on which autopsies were performed twenty-four hours after the hearts had received injections except that in the animals receiving heparin neither macroscopic nor microscopic thrombi were found. The authors pointed out that it is probable that after clinical coronary thrombosis several days must elapse before necrosis becomes sufficiently severe to induce the formation of mural thrombi and that thrombi might be prevented, therefore, even if the administration of heparin was started some considerable time after the initial thrombosis. Just how long the administration of heparin must be continued to permit a degree of healing such that thrombosis is no longer likely to occur must be decided by clinical trial. We agree that a clinical trial is justified, but certain complications and hazards must be kept in mind. In man the development of cardiac infarction is sometimes a gradual or intermittent process, and the onset of symptoms need not necessarily herald the onset of infarction. Thus, it is possible that mural thrombi may already be present at the time of onset of severe symptoms, before the indication for heparin is clear. Moreover, since fresh mural thrombi are sometimes laid down weeks to months after the acute infarction has occurred, the administration of heparin, to be certainly effective, might have to be continued for a very long period of time. And, incidentally, one may well hesitate to add the strain and potential danger of heparin therapy even for a short time to the condition of a patient very ill with acute coronary thrombosis.

Manning, McEachern and Hall [53] describe some interesting observations following sudden occlusion of coronary arteries in dogs. When the anterior descending branch of the left coronary artery was occluded, the mortality was less than 10 per cent for anesthetized dogs and about 40 per cent for conscious ones. The mortality following sudden occlusion of the left circumflex branch was found to be 25 per cent with anesthesia and about 75 per cent without. Satisfactory proof of the cause of the

53. Manning, G. W.; McEachern, C. G., and Hall, G. E.: Reflex Coronary Artery Spasm Following Sudden Occlusion of Other Coronary Branches, Arch. Int. Med. **64**:661 (Oct.) 1939.

greater mortality in the conscious animals is not given. There is evidence that it is not the result of changes in the systemic blood pressure, but the authors believe there may be a reflex spasm of collateral arterioles and small arteries producing additional areas of ischemia.

Controversy [54] continues to rage over the question of the possible precipitating factors in occlusion of a coronary artery. This question is of the first importance from both the scientific and the practical point of view, and fruitful discussion should be welcomed. The whole problem bristles with difficulties and is not likely to be resolved at once. It is highly doubtful if purely clinical studies will provide more than a partial answer, and they may even be misleading. This is so, in part at least, because of the uncertain time relation between the beginning of coronary occlusion and myocardial infarction. One cannot help being impressed with the fact that many persons with marked coronary atherosclerosis never suffer acute coronary occlusion and cardiac infarction. This being so, there must be precipitating factors of coronary occlusion; the occlusion cannot be regarded as a purely fortuitous event.

Two papers [55] have appeared on myocardial infarction not due to frank occlusion of a coronary artery. Undoubtedly this is a more common phenomenon than is ordinarily supposed; Friedberg and Horn noted it in 31 per cent of the last 1,000 autopsies performed in cases of myocardial infarction. It occurs most commonly in the presence of pulmonary embolism, calcific aortic stenosis and marked coronary narrowing.

Mallory, White and Salcedo-Salgar [56] made an important study on the speed of healing of myocardial infarcts, based on 72 autopsies. They describe the characteristic gross and microscopic features of infarcts of various ages and state that the age of an infarct can be judged fairly accurately during the first three weeks but not thereafter. The size and position of the infarct and the state of the remaining myocardial circulation are important determinants of the speed of healing. It was found that small infarcts heal in about five weeks and large

54. Master, A. M.; Dack, S., and Jaffe, H. L.: Age, Sex and Hypertension in Myocardial Infarction Due to Coronary Occlusion, Arch. Int. Med. **64**:767 (Oct.) 1939; Activities Associated with the Onset of Acute Coronary Artery Occlusion, Am. Heart J. **18**:434, 1939. Boas, E. P.: Angina Pectoris and Cardiac Infarction from Trauma or Unusual Effort, with a Consideration of Certain Medicolegal Aspects, J. A. M. A. **112**:1887 (May 13) 1939.

55. Friedberg, C. K., and Horn, H.: Acute Myocardial Infarction Not Due to Coronary Artery Occlusion, J. A. M. A. **112**:1675 (April 29) 1939. Gross, H., and Sternberg, W. H.: Myocardial Infarction Without Significant Lesions of Coronary Arteries, Arch. Int. Med. **64**:249 (July) 1939.

56. Mallory, G. K.; White, P. D., and Salcedo-Salger, J.: The Speed of Healing of Myocardial Infarction, Am. Heart J. **18**:647, 1939.

ones in about eight. Rupture of the heart is most common during the first week, may occur during the second but is rare thereafter. The subendocardial muscle layer often escapes, and another interesting finding is that the age of a mural thrombus is often much less than the age of the infarct itself, i. e., that mural thrombi may be laid down over old infarcts, especially if there is aneurysmal dilatation, weeks or months after the original dilatation.

Cardiac Aneurysm.—Last year we mentioned briefly a paper by Parkinson, Bedford and Thomson [57] on cardiac aneurysm. Their report deserves fuller discussion in connection with the increased interest in the subject. They trace the evolution of our knowledge concerning this condition, pointing out that up to 1914 only 3 reported cases of cardiac aneurysm had been correctly diagnosed during life. From an analysis of published statistics it appears that cardiac aneurysm occurred in 9 per cent of cases of cardiac infarction examined at autopsy. In 13 of the authors' 16 cases the cardiac aneurysm was due to coronary occlusion; in 11 the left anterior descending branch was occluded. In the remaining 3 cases it was associated with rheumatic heart disease. Other relatively common causes are syphilitic, congenital or traumatic heart disease. The most common sites of ventricular aneurysm are the apex and the anterior wall of the left ventricle. Incidentally, it is the opinion of the reviewers that a slight degree of aneurysmal dilatation of the left ventricle in the region of the myocardial infarct from coronary thrombosis is a common finding, though large sacs are infrequent.

There are few characteristic symptoms or signs of ventricular aneurysm, the diagnosis being made usually with the aid of the roentgen ray. Typically, ventricular aneurysm appears a week or two after cardiac infarction, and there may be pain over the apex of the heart. There may be palpable a pulsation over the aneurysm separate and distinct from the apical pulsation. The heart sounds are often faintly heard or muffled, and it is of interest that the first case correctly diagnosed (Remlinger, 1896) exhibited a double murmur presumably due to blood passing in and out through the mouth of the aneurysmal sac.

Parkinson and his associates did not describe any distinctive electrocardiographic features of cardiac aneurysm but noted the common occurrence of tracings indicating cardiac infarction. Nordenfelt [58] and Eliaser and Konigsberg [59] describe certain electrocardiographic charac-

57. Parkinson, J.; Bedford, D. E., and Thomson, W. A. R.: Cardiac Aneurysm, Quart. J. Med. **7**:455, 1938.

58. Nordenfelt, O.: The Electrocardiogram in Chronic Aneurysm of the Heart, Acta med. Scandinav. **102**:101, 1939.

59. Eliaser, M., Jr., and Konigsberg, J.: Electrocardiographic Findings in Cases of Ventricular Aneurysm, Arch. Int. Med. **64**:493 (Sept.) 1939.

teristics which they believe to be presumptive evidence of ventricular aneurysm. Nordenfelt advances the suggestion that often electrocardiograms taken of a patient with a large chronic aneurysm on the anterior wall of the ventricle will show relatively low R waves in lead I, prominent S waves in leads II and III, elevated ST segments in all leads, inversion of the T waves, in lead I, and upright T waves in leads II and III. There may be prominent Q waves in lead I. In lead IV the R waves are absent and the ST segments elevated. Eliaser and Konigsberg found that in over a fourth of the cases of aneurysm of the left ventricle the electrocardiogram shows inversion of the chief initial ventricular deflection and the T waves in lead I with the P waves remaining upright. In over a third of the cases the electrocardiogram shows inversion of the chief initial ventricular deflection in leads II and III and a corresponding upright deflection in lead I that may or may not be of low amplitude.

Of chief importance in the diagnosis of cardiac aneurysm are the roentgenologic findings, which are summarized by Parkinson and his associates as follows:

1. Enlargement of the left ventricle with deformity of its contour.
2. A localized protuberance inseparable from the heart shadow on rotation of the patient.
3. Abnormal or absent pulsation of the aneurysmal zone.
4. Evidence of adhesions between the heart and the chest wall or diaphragm.
5. Calcification of the wall of the sac or of its contained clot.

We should like to refer also to the roentgeno-kymographic findings of absence of pulsation of, or paradoxic pulsation of, cardiac aneurysms as a diagnostic aid in myocardial infarction.

Angina Pectoris.—A number of papers[60] have been published on various clinical aspects of angina pectoris. Of particular interest is the

60. (*a*) Müller, C.: Angina Pectoris in Hereditary Xanthomatosis, Arch. Int. Med. **64**:675 (Oct.) 1939. (*b*) Spillane, J. D., and White, P. D.: Herpes Zoster and Angina Pectoris, Brit. Heart J. **1**:291, 1939. (*c*) Gilbert, N. C.: Vasomotor Changes in the Coronary Arteries and Their Possible Significance, J. A. M. A. **113**:1925 (Nov. 25) 1939. (*d*) Katz, L. N., and Lindner, E.: The Reaction of the Coronary Vessels to Drugs and Other Substances, ibid. **113**: 2116 (Dec. 9) 1939. (*e*) Mainzer, F.: Persistent Pain Localized at a Distance From the Heart (Shoulder, Epigastric Region) in Coronary Insufficiency, Acta med. Scandinav. **101**:541, 1939. (*f*) Wahlberg, J.: Esophageal Spasm as Cardiac Symptom, ibid. **101**:568, 1939. (*g*) Clerc, A., and Sterne, J.: 1262 F. (Diethyl-Amino-Ethoxy-2-Diphenyl) in Treatment of Anginal Syndromes, Presse méd. **47**:1517, 1939. (*h*) Brumm, H. J., and Willius, F. A.: The Surgical Risk in Patients with Coronary Disease, J. A. M. A. **112**:2378 (June 10) 1939. (*i*) White, P. D.: The Immediate and Ultimate Prognosis in Heart Disease with Especial Reference to "Permanent Total Disability," ibid. **112**:2380 (June 10) 1939. (*j*) Sprague, H. B.: Mental Adjustments to Heart Disease: The Factors Involved in Disability, ibid. **112**:2384 (June 10) 1939.

report of Müller on the relationship between angina pectoris and hereditary xanthomatosis. He studied 76 cases of xanthomatosis; in 68 there was associated heart disease, and a diagnosis of angina pectoris was made in 59. Müller points out that the syndrome of cutaneous xanthomatosis, hypercholesteremia and angina pectoris presents itself as a well defined clinical disease at an early age and that it may be transmitted as a dominant hereditary disease.

Spillane and White [60b] describe 12 instances of the occurrence of herpes zoster in anginal subjects. In 10 of these the herpetic eruption appeared after the anginal attacks had become established, while in the remaining 2 it appeared about two years before the angina. In every instance there was a close relationship between the distribution of the eruption and that of the anginal pain. It is suggested that repeated bombardment of spinal root ganglions by afferent impulses from the ischemic heart gives rise to antidromic impulses that lead to the formation of blisters.

There has been continued interest in surgical procedures designed for the relief of angina pectoris.[61] Raney [61b] reports amazing success in the relief of pain by section of the rami communicantes (2-5) from the intercostal nerves and section of the sympathetic chain between the fifth and sixth dorsal ganglions on the left side. Unfortunately, most of the report is concerned with rather unimpressive arguments attempting to justify the procedure on theoretic grounds. Except for 2 case reports, only meager clinical details are given. Eleven patients with "desperate attacks" of angina pectoris were all completely relieved of pain by means of the aforementioned operation.

SPONTANEOUS MEDIASTINAL EMPHYSEMA

This syndrome [62] is mentioned here because of the importance of differentiating it from acute cardiac infarction. In fact, Hamman's [62a] first case was so diagnosed at the time of onset of symptoms. This author has summarized the essential clinical features as follows:

1. Interstitial emphysema of the lung may occur without the least effort, when the patient is quietly standing, sitting or lying down.

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61. (*a*) O'Shaughnessy, L.; Slome, D., and Watson, F.: Surgical Revascularisation of the Heart: The Experimental Basis, Lancet **1**:617, 1939. (*b*) Raney, R. B.: A Hitherto Undescribed Surgical Procedure Relieving Attacks of Angina Pectoris: Anatomic and Physiologic Basis, J. A. M. A. **113**:1619 (Oct. 28) 1939.

62. (*a*) Hamman, L.: Spontaneous Mediastinal Emphysema, Bull. Johns Hopkins Hosp. **64**:1, 1939; (*b*) A Note on the Mechanism of Spontaneous Pneumothorax, Ann. Int. Med. **13**:923, 1939. (*c*) McGuire, J., and Bean, W. B.: Spontaneous Interstitial Emphysema of the Lungs, Am. J. M. Sc. **197**:502, 1939.

2. When the air reaches the mediastinum, distending the mediastinal tissues the patient complains of pain which is often very severe. Usually the pain is located beneath the sternum; sometimes it radiates to the back; at other times to the neck and shoulders, rarely to the arms. Accompanying the pain there is often a sensation of pressure or of expansion beneath the sternum.

3. There are no constitutional symptoms, no evidence of shock. The temperature, the pulse and respiratory rates, the blood pressure, the leucocyte count are very little if any altered.

4. In many instances a peculiar and distinctive sound is heard over the heart synchronous with its contractions. Usually the sound is heard only during systole but at times it may be heard also during diastole.

5. The area of cardiac dulness is diminished or completely obliterated, the dulness being replaced by a hyperresonant percussion note.

6. Pneumothorax often occurs. The pneumothorax is usually small and may not be suspected until a roentgenogram of the chest has been taken. . . .

7. The roentgenogram is a valuable aid in establishing the diagnosis. In instances in which the characteristic sound over the heart is absent the roentgenographic evidence of air in the mediastinum may be decisive.

8. When air appears in the subcutaneous tissues of the neck the diagnosis is at once assured.

GLYCOGEN DISEASE

Van Creveld [63] has written a comprehensive treatise on glycogen disease, which includes a section on cardiomegalia glycogenica. He points out the importance of this condition in explaining many cases of so-called congenital idiopathic hypertrophy of the heart. He states that glycogen disease should be suspected when, at examination, a child is found to have a large heart without valvular lesions or an anomaly of development of which the enlargement may be the consequence.

HEART DISEASE RESULTING FROM DEFORMITIES OF THE CHEST

Chapman, Dill and Graybiel [64] have sought to describe and explain the decrease in functional capacity of the lungs and heart resulting from deformities of the chest. Persons so afflicted in youth are usually dwarfed, and their activity is limited. Dyspnea, palpitation and fainting attacks are common symptoms, and tachycardia, low blood pressure and accentuation of the pulmonary second sound are commonly observed. A sudden aggravation of symptoms usually serves as a warning that death is near, for the cardiopulmonary reserve is low. The authors emphasize that depressants of respiratory function, such as morphine, are poorly tolerated and have been known to cause death in patients with severe deformity.

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63. van Creveld, S.: Glycogen Disease, Medicine **18**:1, 1939.

64. Chapman, E. M.; Dill, D. B., and Graybiel, A.: The Decrease in Functional Capacity of the Lungs and Heart Resulting from Deformities of the Chest: Pulmonocardiac Failure, Medicine **18**:167, 1939.

GRANULOMATOUS MYOCARDITIS

Jonas [65] reports his observations in 5 cases in which the myocardium and other tissues were involved in a granulomatous process characterized by tubercle-like foci with giant cells, necrosis and mononuclear cell infiltration. Careful studies did not reveal any evidence to indicate an etiologic relation to tuberculosis or syphilis. The author discusses these 5 cases in relation to somewhat similar cases already on record.

PERIPHERAL VASCULAR COLLAPSE

During 1939 a number of papers have been published by a single group of workers describing their studies on the functioning of the peripheral vascular system.[66] Their findings are of considerable clinical interest and are important in the diagnosis and proper treatment of peripheral circulatory collapse. These authors have shown that loss of venous tone with consequent pooling of blood is the mechanism responsible for the common type of circulatory collapse. This form of collapse must be distinguished from that which is associated with cachexia or acute loss of blood. The results of their experiments indicate that paredrinol (α-N-dimethyl-p-hydroxyphenethylamine) has as one of its chief actions the elevation of venous tone without at the same time increasing the metabolism of the tissues or causing marked arteriolar constriction. Thus, in cases of shock in which the volume of blood is adequate the administration of paredrinol results in a primary increase in venous tone and an emptying of the splanchnic reservoirs, thereby causing increased venous return to the heart. It is important to point out that in the type of collapse associated with small volume of blood and without venous pooling paredrinol not only is of no value but is contraindicated, as are epinephrine and pitressin, drugs commonly used in the past.

HEART FAILURE AND ITS TREATMENT

It is obviously impossible even to mention by title the large number of worth while articles relating to cardiac failure. Only a few touching on subjects of broad interest have been chosen for review.

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65. Jonas, A. F., Jr.: Granulomatous Myocarditis, Bull. Johns Hopkins Hosp. **64**:45, 1939.

66. Stead, E. A., Jr.; Kunkel, P., and Weiss, S.: Effect of Pitressin in Circulatory Collapse Induced by Sodium Nitrite, J. Clin. Investigation **18**:673, 1939. Stead, E. A., Jr., and Kunkel, P.: Mechanism of the Arterial Hypertension Induced by Paredrinol (α-N-Dimethyl-p-Hydroxyphenethylamine), ibid. **18**: 439, 1939. Kunkel, P.; Stead, E. A., Jr., and Weiss, S.: Effect of Paredrinol (α-N-Dimethyl-p-Hydroxyphenethylamine) on Sodium Nitrite Collapse and on Clinical Shock, ibid. **18**:679, 1939. Kunkel, P., and Stead, E. A., Jr.: Blood Flow and Vasomotor Reactions in the Hand, Forearm, Foot, and Calf in Response to Physical and Chemical Stimuli, ibid. **18**:225, 1939.

The effect of heart failure on the coronary circulation is a factor often neglected or poorly understood. Visscher[67] ably discusses this effect and points out that fundamentally in all forms of progressive heart failure there are restrictions of the total possible coronary flow. The effects of sudden or gradual occlusion of the coronary vessels are well known, but the restriction of coronary flow produced by elevations in pressure in those cavities into which the coronary venous blood drains is not generally appreciated. Visscher gives experimental data which show that the greater the difference in blood pressure between the aorta and the pulmonary artery the greater the thebesian flow and the less the coronary sinus flow. Also, the greater the difference in blood pressure between the aorta and the coronary sinus, other factors being held constant, the greater the coronary sinus flow. Now it has been shown that the right circumflex artery, which supplies mainly the right ventricular muscle, drains almost exclusively through the right thebesian systems into the right side of the heart. The thebesian flow in the left side of the heart is relatively small, and the blood can reach the left ventricular cavity only during diastole, because only then is the pressure gradient suitable. On the other hand, blood can leave thebesian channels into the right ventricle, both in systole and in diastole, because there is a positive pressure gradient at all times. As a result, it is the right ventricle which will be most seriously affected by a restriction of thebesian flow. Anything which increases right intraventricular pressure accelerates heart failure by the restriction of coronary flow which occurs. The author points out the familiar fact that the left side of the heart can carry enormous loads, as in hypertension and in valvular disease, for many years, whereas when the right ventricle works against increased loads the heart may fail rapidly.

The restandardization of digitalis in 1936, increasing its potency, has caused a great deal of confusion not only among pharmacologists but among physicians prescribing the drug. Before this revision the strength was such that ordinarily after a patient was digitalized one pill (1½ grains, or 0.095 Gm.) daily sufficed to maintain its action. In 1936 the United States Pharmacopeial Committee of Revision adopted the international powder as a standard for this country. This has resulted in an increase of from 25 to 30 per cent in the strength of powdered digitalis U. S. P. and of tincture of digitalis U. S. P. The many conflicting reports of the potency of the U. S. P. XI digitalis have been due, according to Edmunds,[68] to faulty calculation or technic

67. Visscher, M. B.: The Restriction of the Coronary Flow as a General Factor in Heart Failure, J. A. M. A. **113**:987 (Sept. 9) 1939.

68. Edmunds, G. W.: The Potency of Digitalis Preparations of the 1936 Pharmacopeia, J. A. M. A. **113**:284 (July 22) 1939.

in standardization. Although there are certain theoretic advantages in international uniformity of such an important drug as digitalis, yet in this country the practical use of 1½ grain (0.095 Gm.) pills has been rendered more difficult. This is so because with routine administration "one pill a day" is often too much. A simple solution might be to reduce the size of the pill. However, as the matter now stands, this fact of increased digitalis potency must be kept in mind.

For many years the administration of digitalis in heart failure with normal rhythm was a controversial matter, especially in England. It is interesting, therefore, to review the investigations of Gavey and Parkinson,[69] which were undertaken primarily with this question in mind. Sixty-five patients with heart failure and normal rhythm were observed. The control lay in a preliminary rest in bed without digitalis, and, for comparison, another series of 30 patients with heart failure and auricular fibrillation were observed in the same way. The results indicate that 60 per cent of the patients with normal rhythm improved following the administration of digitalis; the improvement was slight in 29 per cent and moderate or marked in 31 per cent. Of the patients with auricular fibrillation, clinical improvement was demonstrated in 72 per cent. If the group with rheumatic heart disease is left aside, the fibrillation series responded to digitalis no better than the normal rhythm series. In other words, the real difference in response of heart failure to digitalis lies not between auricular fibrillation and normal rhythm but rather between rheumatic auricular fibrillation and all other kinds of heart failure irrespective of rhythm. The authors state that digitalis is always indicated in congestive heart failure, irrespective of rhythm, but that it is often inefficient, as it fails completely in about one third of all cases.

Another controversial question regarding the use of digitalis is whether or not it should be given to patients with partial heart block. Blumgart and Altschule[70] record their observations on 19 patients with congestive failure and partial heart block during digitalization. Of the 19, 11 showed no change in the PR interval, in 7 the PR interval was lengthened, and in 1 it was shortened. In 1 case occasional 2 to 1 heart block disappeared, and in all the rest there were no alterations in the orderly sequence of auriculoventricular contractions. They conclude that digitalis in therapeutic amounts may be safely given in cases of partial heart block but add the warning that caution and careful observation should be exercised.

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69. Gavey, C. J., and Parkinson, J.: Digitalis in Heart Failure with Normal Rhythm, Brit. Heart J. **1**:27, 1939.

70. Blumgart, H. L., and Altschule, M. D.: Should Digitalis Be Administered to Patients with Preexisting Partial Heart Block? Am. J. M. Sc. **198**:455, 1939.

Boothby, Mayo and Lovelace [71] give the indications for, and the method of administration of, 100 per cent oxygen. They point out that the administration of 100 per cent oxygen will significantly increase the power of the blood to transport oxygen and that it may be given safely in continuous fashion over a period of two days. We should like to call attention to the fact that pure oxygen has been shown to be highly irritating to the respiratory mucosa and that the absence of any symptoms when the "B. L. B. apparatus" (devised by the investigators just mentioned) is used suggests that a concentration of 100 per cent oxygen is not reached.

71. Boothby, W. M.; Mayo, C. W., and Lovelace, W. R.: One Hundred Per Cent Oxygen: Indications for Its Use and Methods of Its Administration, J. A. M. A. **113**:477 (Aug. 5) 1939.

Book Reviews

Rheumatism. By H. Warren Crowe, M.D. (Oxon), B.Ch., M.R.C.S., L.R.C.P. Pp. 280, with 31 illustrations. Price, 12s. 6d., cloth. London: John Bale Sons & Curnow, Ltd., 1939.

It is difficult to write a good book on the subject of rheumatism, and it is almost certain that any book on this subject will provoke argument. Dr. Crowe has written an excellent book, but it will not meet with universal agreement. In writing such a book, one of the most difficult tasks is to arrange a nomenclature so that the writer and the reader may meet on common ground. Dr. Crowe has met this challenge very skilfully. He has drawn on the classifications of the British Commission, the American Commission and the Ministry of Health, with none of which he fully agrees. He succeeds well in making his subject matter clear to one who is accustomed to the use of different terms.

After dealing with the matter of nomenclature, he continues with a discussion of differential diagnosis, pathology and etiology. This is well done and is quite orthodox until the section on etiology is reached. All are familiar with Dr. Crowe's ideas about the infectious nature of rheumatism, and these ideas are fully expounded in the section on etiology. The ideas are of course carried over into the discussion of treatment in which the author's original work in vaccine treatment is discussed.

There are additional chapters on physical therapy, roentgen ray therapy and the orthopedic treatment of rheumatism. The concluding chapter deals with laboratory technic and the technic of physical therapy.

This book may be recommended as a carefully constructed piece of work that is the result of long and careful observation of many patients who have suffered from this disease. The author mentions the "nebulous conception of rheumatism." This work will no doubt serve as one of the instruments to dispel the cloud that surrounds the subject.

Failure of the Circulation. By Tinsley R. Harrison, M.D., Associate Professor of Medicine, Vanderbilt University School of Medicine. Second edition. Price, $4.50. Pp. xiv + 502, with 59 figures and 22 tables. Baltimore: The Williams & Wilkins Company, 1939.

The first edition of this book was published in 1935. It was deservedly successful. A reviewer (*J. A. M. A.* **105**:1141 [Oct. 5] 1935) remarked that the book presented clinical cardiologists with the latest applications of the altered physiologic function in heart failure and recommended that all internists read it. The review in the Archives of Internal Medicine (**57**:643 [March] 1936) was equally complimentary. Here it was said that the book not only discussed the theoretic aspects of heart failure in a thoroughly satisfactory manner but also contained a great deal of practical advice concerning the diagnosis and treatment of heart disease. It was an authoritative treatise. Both reviews were the leading ones in the issues of the periodicals in which they appeared.

The second edition follows the general pattern of the first, with certain modifications, and is a trifle over a hundred pages longer. The author has been careful as to how his book was allowed to grow. He has made a conscientious effort to strengthen the first edition in all its weak spots. Most of the extra pages, however, are due to new ideas. The increased length of the book reflects very clearly the activity of workers in the field of cardiology and the rapidity with which new knowledge has been built up.

Once more this book deserves high praise. Like the first edition, the second presents clinical cardiologists with the latest applications of the physiologic conceptions of heart failure. Cardiologists, students and practitioners all will find it interesting, informative and stimulating.

Medizinische Praxis: Sammlung für ärtztliche Fortbildung. Volume 27. By M. Ratschow. Mit einem Geleitwort von R. Cobet. Price, 9.75 marks. Pp. 193, with 46 illustrations. Dresden: Theodore Steinkopff, 1939.

This most recent (twenty-seventh) volume of the "Medizinische Praxis" series is concerned with peripheral vascular disturbances. After briefly defining these conditions and succinctly reviewing their historic development, the author describes the anatomy and physiology of peripheral blood vessels. A fairly complete consideration of the various diagnostic methods used in studying the organic and functional changes in the peripheral vessels is presented. The characteristic clinical manifestations of the various types of peripheral vascular diseases are described and their management stated. Obviously, completeness of detail cannot be achieved in a short monograph on a subject the literature of which has now assumed voluminous proportions. Thus a mere paragraph on thrombophlebitis is woefully inadequate. However, the book serves as a quick reference for the student and general practitioner. There are forty-six illustrations, consisting of charts, diagrams, photographs, photomicrographs and arteriograms. An incomplete but fairly representative and up-to-date bibliography is included. There is also an author and a subject index.

Annual Review of Physiology, Volume 1. Editor, J. Murray Luck and associate editor, Victor E. Hall. Price, $5.00. Pp. 709. Stanford University, California: Stanford University Press, 1939.

The need for reviews and compendia of medical literature becomes more and more evident each year. Volume 1 of the *Index Medicus,* in 1927, contained 820 pages, whereas volume 20, in 1936, had extended to no less than 1499. The "Annual Review of Physiology," of which the first volume has recently appeared, seems therefore to be inevitable, and one is pleased to find that Murray Luck, veteran of the Annual Review of Biochemistry, is in charge also of this latest physiologic review. Twenty-four articles by authorities in the various branches of physiology fill a volume of some 700 pages. As many as four or five hundred references follow some of the articles. My only criticism—or rather comment—is that in some of the contributions the material is so condensed that it makes poor reading, and the volume is really a succession of abstracts; but when a year's output of work is condensed into one volume this is hardly to be avoided.